Vol. 226, No. 2 AUGUST, 1953 No. 976

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.
ESTABLISHED 1820

Editor
RICHARD A. KERN, M.D.

Associate Editor
THOMAS M. DURANT, M.D.

Assistant Editor
CHRIS J. D. ZARAFONETIS, M.D

Carl Bachman	G. Lyman Duff	John E. Gordon	P. R. A. May	I. S. Ravdin
Herman Beerman	Franklin G. Ebaugh	David M. Gould	R. H. Morgan	C. Thorpe Ray
Wm. L. Benedict	Cary Eggleston	Theodore H. Ingalls	E. G. D. Murray	John H. Stokes
A. M. Bongiovanni	Noah D. Fabricant	N. R. Ingraham, Jr.	A. Harry Neffson	H. P. Wagener
George E. Burch	Harry Gold	C. G. Johnston	Franklin L. Payne	Irving J. Wolman

Limitations in the Use of Gamma Globulin in Poliomyelitis. By WILLIAM McD. HAMMON, M.D. 125

Sarcoidosis in the Armed Forces. By ROBERT S. NELSON, Col. MC USA 131

Hyaluronidase and the Subcutaneous Administration of Electrolyte-Free Glucose Solution. By F. M. MATEER, M.D., K. L. GARVER, M.D., M. J. SAKOL, M.D., and T. S. DANOWSKI, M.D. 139

The Medical Aspects of Electric Shock Therapy (Including a Study of 192 Patients). By EDMOND H. NIESEN, JR., M.D. 143

Psittacosis. By W. W. G. MACLACHLAN, M.D., G. E. CRUM, M.D., R. F. KLEINSCHMIDT, M.D., and P. F. WEHRLE, M.D. 157

A Comparative Study of the Effects of Three Vasodilator Drugs, Pentamethonium Bromide (C-5), Dilatol (SKF-1700-A) and Pendiomide (BA-9295) on the Digital Cutaneous Blood Flow. By HERBERT L. NEEDLEMAN, M.D., and ORVILLE HORWITZ, M.D. 164

Oral Therapy with Mercumatilin (Cumertilin), A New Mercurial Diuretic. By B. E. POLLOCK, Col., MC USA, and FRANCIS W. PRUITT, Col., MC USA 172

Occupation as a Factor in the Community Health Hazards of Air Pollution. By C. A. MILLS, M.D. 177

Some Effects of Nitrogen Mustard and Triethylene Melamine in Acute Disseminated Lupus Erythematosus. By ROBERT J. ROHN, M.D., and WILLIAM H. BOND, M.D. 179

Preservation of Platelets. By JAMES L. TULLIS, M.D. 191

The Use of ACTH in Preparing Patients with Idiopathic Thrombocytopenic Purpura for Splenectomy. By RICHARD W. GREENE, M.D., WILLIAM W. FALOON, M.D., and EUGENE L. LOZNER, M.D. 203

Progress of Medical Science

Surgery—Recent Advances in the Knowledge of the Mechanism, Diagnosis and Treatment of Head Injury. By E. S. GURDJIAN, M.D., and J. E. WEBSTER, M.D. 214

Ophthalmology—Ophthalmologic Diagnosis of Meningiomas of the Sphenoidal Ridge. By THOMAS P. KEARNS, M.D., and HENRY P. WAGENER, M.D. 221

Proceedings of the Physiological Society of Philadelphia 229

Complete contents on adv. page 10

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

COPYRIGHT, 1953, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AS SECOND-CLASS MATTER NOVEMBER 5, 1887 AT THE POST OFFICE AT PHILADELPHIA, PA. UNDER THE ACT OF MARCH 3 1879
PUBLISHED MONTHLY. SUBSCRIPTIONS, TEN DOLLARS A YEAR

When Blood Pressure Soars to Dangerous Heights

You can depend on Hepvisc to reduce readings to safer levels, as well as to bring your patients gratifying relief from the subjective symptoms.

AVERAGE BLOOD PRESSURE BY AGE (Auscultatory Method)

AGE	Under 18	18-22	23-27	28-32	33-37	38-42	43-47	48-52	53-57	58-62	63 +
SYSTOLIC Male	117.0	120.2	121.2	121.8	122.9	124.3	126.0	128.1	130.3	131.9	134.2
Female	114.7	116.4	117.7	118.7	120.4	123.6	127.1	129.8	132.5	133.7	135.4
DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

**Fourth phase

*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

···HEPVISC REG. U. S. PAT. OFF.

Hexanitrate of Mannitol + Viscum Album

Available in Bottles of 50-500-1000 tablets.

Complete Literature and Professional Samples Sent upon Request

THE ANGLO-FRENCH DRUG CO. (U.S.A.) LTD.

75 Varick St., New York 13, N. Y.

for your
peptic ulcer
patients...

Antrenyl T.M.

bromide

OXYPHENONIUM BROMIDE CIBA

New High Potency
Anticholinergic with
No Bitter Aftertaste

As adjunctive therapy in your standard peptic ulcer regimen*, Antrenyl offers potent anticholinergic action to inhibit motility of the gastrointestinal tract and gastric secretion.

Although Antrenyl is one of the most potent of all anticholinergic agents, it rarely causes esophageal or gastric irritation and has no bitter aftertaste. In individualized doses, it is well tolerated and side effects are absent or generally mild.

In one study[1] patients receiving Antrenyl obtained relief from acute symptoms within 24 to 36 hours. Dosage was individually adjusted at 5 to 10 mg. four times a day. Side effects were adjudged less pronounced than those of other similar agents ordinarily used in the management of peptic ulcer.

Prescribe Antrenyl in your next case of peptic ulcer and spasm of the gastrointestinal tract. Available as tablets, 5 mg., scored, bottles of 100; and syrup, 5 mg. per teaspoonful (4 cc.), bottles of 1 pint.

Ciba Pharmaceutical Products, Inc., Summit, N. J.

**Leading gastroenterologists recommend:*

rest
sedation
antacids
nonirritating diet
anticholinergics

Ciba

1. Rogers, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:180, 1952.

2/1896M

CONTENTS

ORIGINAL ARTICLES

Limitations in the Use of Gamma Globulin in Poliomyelitis
By William McD. Hammon, M.D., Pittsburgh, Pennsylvania.

Sarcoidosis in the Armed Forces
By Robert S. Nelson, Col. MC USA, Munich, Germany.

Hyaluronidase and the Subcutaneous Administration of Electrolyte-Free Glucose Solution
By F. M. Mateer, M.D., K. L. Garver, M.D., M. J. Sakol, M.D., and T. S. Danowski, M.D., Pittsburgh, Pennsylvania.

The Medical Aspects of Electric Shock Therapy (Including a Study of 192 Patients)
By Edmond H. Niesen, Jr., M.D., Louisville, Kentucky and Cincinnati, Ohio.

Psittacosis
By W. W. G. Maclachlan, M.D., G. E. Crum, M.D., R. F. Kleinschmidt, M.D., and P. F. Wehrle, M.D., Pittsburgh, Pennsylvania.

A Comparative Study of the Effects of Three Vasodilator Drugs, Pentamethonium Bromide (C-5), Dilatol (SKF-1700-A) and Pendiomide (BA-9295) on the Digital Cutaneous Blood Flow
By Herbert L. Needleman, M.D., and Orville Horwitz, M.D., Philadelphia, Pennsylvania.

Oral Therapy with Mercumatilin (Cumertilin), A New Mercurial Diuretic
By B. E. Pollock, Col., MC USA, and Francis W. Pruitt, Col., MC USA, San Francisco, California.

(Contents continued on page 12)

Metrazol Council Acc

Powerful, Quick Acting Central Stimula

ORALLY - for respiratory and circulatory support
BY INJECTION - in the emergency

AMPULES - 1 and 3 cc. (each cc. contains 1½ gra
TABLETS - 1½ grains.
ORAL SOLUTION - (1½ grains per cc.)

Metrazol, brand of pentamethylentetrazol, Trade Mark Reg. U. S. Pat. Off.

BILHUBER-KNOLL CORP. ORANGE, NEW JERSE

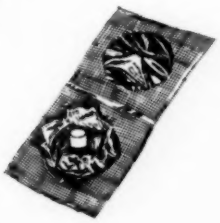
Which aged patient has PA...?

Pernicious anemia is basically a disease of older people. Although none of the aged patients depicted here may have pernicious anemia, it is very likely that all of them have deficient secretion of intrinsic factor, which in extreme cases would result in pernicious anemia. Among the many functions of the human organism which slow down as we advance in age is the stomach's secretion of intrinsic factor. Assure a full quota of intrinsic factor and its essential partner, vitamin B_{12}, for your aged patients by prescribing Bifacton. Only two tiny Bifacton tablets constitute a full U.S.P. anti-anemia unit, sufficient for maximal daily replacement of intrinsic factor and vitamin B_{12}.

BIFACTON®

The *Only* Intrinsic Factor Product
Recognized and Approved
by the U.S.P. Anti-Anemia Board

Bifacton tablets are available in boxes of 30, specially stripped in hermetically sealed aluminum foil.



Organon INC. · ORANGE, N. J.

Bifacton Patent Pending

CONTENTS (*Continued*)

Occupation as a Factor in the Community Health Hazards of Air Pollution 177
By C. A. Mills, M.D., Cincinnati, Ohio.

Some Effects of Nitrogen Mustard and Triethylene Melamine in Acute Disseminated Lupus Erythematosus 179
By Robert J. Rohn, M.D., and William H. Bond, M.D., Indianapolis, Indiana.

Preservation of Platelets 191
By James L. Tullis, M.D., Boston, Massachusetts.

The Use of ACTH in Preparing Patients with Idiopathic Thrombocytopenic Purpura for Splenectomy 203
By Richard W. Greene, M.D., William W. Faloon, M.D., and Eugene L. Lozner, M.D., Syracuse, New York.

(*Contents continued on page 14*)

FOR YOUR PATIENT
with
Bronchial Asthma,
Hay Fever, Urticaria

RESTFUL NIGHTS and ACTIVE DAYS

CAPSULES PLAIN *(for prompt action)*

LUASMIN Brewer

TABLETS ENTERIC-COATED *(for delayed action)*

One capsule and one tablet, taken at bedtime will provide almost all patients with eight hours relief and sleep. The relief can be sustained by using the capsules during the day at 4 hour intervals as required.

Each capsule and enteric-coated tablet contains:

Theophylline Sodium Acetate	(3 gr.) 0.2 Gms.
Ephedrine Sulfate	(½ gr.) 30 Mg.
Phenobarbital Sodium	(½ gr.) 30 Mg.

Capsules and tablets in half the above potency available for children and mild cases in adults.

Brewer EST. 1852

For sample—just send your Rx blank marked—12 LUS

BREWER & COMPANY, INC.
WORCESTER 8, MASSACHUSETTS U.S.A.

"Vaginal leukorrhea" due to *Trichomonas vaginalis* is described[1] as "one of our truly nuisance diseases," being present in *one out of five* women, yet many a woman still hesitates to discuss leukorrheal discharge with her physician.

Physiologic Floraquin® Therapy in Leukorrhea

Many a woman also is discouraged because the discharge reappears[2] time after time, even after an apparent cure of weeks or months.

Treatment[3] has a twofold purpose: To destroy the trichomonads and to keep the vagina dry. Floraquin, with its acid and sugar content, maintains a normal vaginal pH of 3.8 to 4.4 and encourages the growth of the normal Döderlein bacilli and secretions.

Active treatment with Floraquin should be continued[4] through at least two or three menstrual periods to assure successful cure.

It is available as powder and vaginal tablets.

1. Savage, M. B., in discussion of Davis, C. H., and Grand, C. G.: Trichomonas Vaginalis Donné: An Evaluation of Experimental and Clinical Data, Am. J. Obst. & Gynec. *64*: 544 (Sept.) 1952.

2. Upton, J. R.: Symposium: Certain Aspects of Office Treatment in Obstetrics and Gynecology: Trichomonas Vaginalis Vaginitis, West. J. Surg. *60*:222 (May) 1952.

3. Kleegman, S. J.: Treatment of Trichomonas Vaginitis, GP *6*:49 (Aug.) 1952.

4. Kanter, A. E.: The Recognition and Treatment of Vaginal Lesions, Postgrad. Med. *12*:457 (Nov.) 1952.

SEARLE *Research in the Service of Medicine*

CONTENTS (*Continued*)

PROGRESS OF MEDICAL SCIENCE

Medicine
(January and July)—G. E. Burch
C. Thorpe Ray

Neurology and Psychiatry
(January and July)—F. G. Ebaugh and
Philip R. A. May

Surgery
(February and August)
I. S. Ravdin and C. G. Johnston

Ophthalmology
(February and August)
W. L. Benedict and H. P. Wagener

Preventive Medicine and Epidemiology
(March and September)
J. E. Gordon and Theodore H. Ingalls

Pathology and Bacteriology
(March and September)
G. Lyman Duff and E. G. D. Murray

Dermatology and Syphilology
(April and October)
J. H. Stokes, H. Beerman and
N. R. Ingraham, Jr.

Oto-Rhino-Laryngology
(April and October)—N. D. Fabricant and
A. Harry Neffson

Radiology
(May and November)—R. H. Morgan and
David M. Gould

Therapeutics
(May and November)
C. Eggleston and H. Gold

Pediatrics
(June and December)—I. J. Wolman and
A. M. Bongiovanni

Gynecology and Obstetrics
(June and December)
C. Bachman and Franklin L. Payne

SURGERY

Recent Advances in the Knowledge of the Mechanism, Diagnosis and Treatment of Head Injury 211
By E. S. Gurdjian, M.D., and J. E. Webster, M.D., Detroit, Michigan.

OPHTHALMOLOGY

Ophthalmologic Diagnosis of Meningiomas of the Sphenoidal Ridge 221
By Thomas P. Kearns, M.D., and Henry P. Wagener, M.D., Rochester, Minnesota.

PHYSIOLOGY

Proceedings of the Physiological Society of Philadelphia, May 19, 1953 229

Book Reviews and Notices 232

The Non-barbiturate Daytime Sedative—

BROMURAL

brand of Bromisovalum (bromisovalerylurea)

Soothes the Nerves, Induces Refreshing Sleep.
5-grain tablets and powder. Dose: 1 to 3 Tablets.

BILHUBER-KNOLL CORP. ORANGE NEW JERSEY

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1953

ORIGINAL ARTICLES

LIMITATIONS IN THE USE OF GAMMA GLOBULIN IN POLIOMYELITIS*†

By William McD. Hammon, M.D., Dr.P.H.

PROFESSOR AND HEAD OF THE DEPARTMENT OF EPIDEMIOLOGY AND MICROBIOLOGY

(From the Department of Epidemiology and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania)

At the present moment, just before the annual poliomyelitis season, we find ourselves for the first time with an agent capable of preventing the paralytic disease[1-4]. Unfortunately, the circumstances under which it is effective are definitely limited and not yet completely defined and furthermore, the agent is in short supply. If the recognized limitations of its application were better understood by physicians and the public there might be much less enthusiasm about it and possibly less demand for it.

Poliomyelitis, as you all recognize, is a peculiar disease: important far beyond its importance. It has been dramatized to the point that when the risk approaches 1 in 1,000 it carries the psychological impact formerly reserved for smallpox or bubonic plague. If this were not the case we could immediately accept gamma globulin in its proper perspective; as a passive, immunizing agent with a very limited field of practical usefulness. The demonstration of its effectiveness is important principally as a stepping stone to something better. However, when one tries to speak in terms of what he considers realism in the scientific, economic and administrative aspects of this problem he is immediately informed by his colleagues and friends that rational, cool calculations of cost versus known risk cannot be tolerated. This is an immunizing agent that would receive little consideration in any other disease of equal importance in death or disability rates, yet it has assumed tremendous importance in poliomyelitis and becomes overnight a $20,000,000 problem requiring emergency handling at a national level. It is apparent that until some better immunizing agent becomes available every possible effort will be made to meet at least a portion of the demand, and we should all be interested in seeing that this material is used as intelligently as possible. Let us attempt to examine the problem briefly.

We all recognize the conditions under which gamma globulin is used in

* Aided by a grant from the National Foundation for Infantile Paralysis

† Read at the Annual Meeting of the Association of American Physicians, Atlantic City, New Jersey, May 5 & 6, 1953.

measles. It is recommended for use only after a recognized exposure in a child known to be susceptible, also in special instances of institutional exposure such as a hospital. Including occasional wasteful use in an ill-advised manner, one might estimate that at least every other injection for measles either prevents or modifies the disease.

Poliomyelitis presents a most striking different set of circumstances. Most infections are not associated with clinically recognized disease; exposure is rarely suspected at the time it occurs and susceptibles needing immunization cannot be readily identified. As a result, under the most select circumstances, hundreds or thousands of injections must be given to provide protection to one or two who may actually profit from it. This is blind, shotgun prevention in the extreme and has no resemblance to any previous application of passive prophylaxis of which I have knowledge.

In the planning of our field experiments, it was decided that the maximum of desired information could be obtained most rapidly and easily by making the test in epidemic areas, injecting all comers from a specified county in a selected age group in as short a period of time as possible, but indiscriminately in respect to time or degree of likely exposure. There was no intent to establish this as a pattern for subsequent, practical use. It was expected that factual information would be obtained which would assist in planning intelligent use. We believe the purpose has been partially accomplished already and that much useful immunologic information is still to come from the laboratory work now in progress on specimens collected during the study. This information, together with knowledge of the epidemiology of the disease should guide us in planning any application. Unfortunately, both immunologic and epidemiologic data are sufficiently incomplete that certain differences in opinion regarding the best possible use are to be expected. Obviously, one cannot wait until all facts are elicited, as some would prefer, before attempting to use gamma globulin. In addition to scientific problems there are no less complicated administrative considerations, and political pressures must be anticipated. In a limited period of time I can do little here but present a few personal opinions without marshaling all the complicated evidence of various types which appears to justify such opinions.

1. Mass or Community Prophylaxis: One can conceive of few uses which could be described as more indiscriminate or wasteful than injection of all persons at one time in a community simply because the incidence of disease has attained unusual proportions. Selection of a limited age group and an attempt to pick an extremely severe epidemic in its early rising phase improve the situation somewhat. We were fortunate enough to select an almost ideal situation for our third field trial, but I would hesitate to try to duplicate it. The total rate attained was approximately 400 per 100,000, and we appear to have prevented one case for each 250 or 300 injections of gamma globulin given. In view of the present public demand, areas such as this, if it were possible to select them with regularity, might well be given gamma globulin. Contrast this, however, with our Harris County, Texas selection, made a few weeks before. This we selected as the most ideal situation we could find in the whole United States up to the first of July. Here we appear to have prevented one case for each 2,000 injections. However, I can envision terrific political pressures for gamma globulin from large communities where even 10,000 to 50,000 doses might prevent

only one case, yet one could not refute the possibility of a severe outbreak at the time the demand was made.

Some have insisted that the results of our experiment only justify subsequent use in mass, community prophylaxis. They state that there is no proof that it will work under any other condition, since the test was conducted in this manner. With this I cannot agree any more than I would agree that because we demonstrated gamma globulin would protect when injected in the right buttock it should not be given in the left buttock until this also is proved to be effective. Regardless of methods employed, those few individuals in the communities used in our studies who were actually protected by the injections were protected because they were exposed shortly before or soon after injection and because they were previously susceptible. The important thing to remember is that exposure and susceptibility are essential criteria for the need of prophylaxis. Surely the sciences of epidemiology and immunology can help us to select with some slight degree of accuracy a few small groups in the population which are most likely to contain such individuals.

2. Family Contacts of Diagnosed Cases: Use in family contacts of diagnosed cases, on the basis of all epidemiologic evidence available, concentrates its use, as in measles, to the most heavily exposed unit of population which can be selected. Use in this manner also avoids the hazards of epidemic prediction and political pressures. Furthermore, it brings some gamma globulin back into communities where blood donations were made rather than to have it all allocated to a very few selected communities. The question is: will gamma globulin, when used thus, be given in time to prevent or modify any more cases per thousand injections than if given simultaneously to all children in the community, or than if used in some other manner? Certain of the limiting factors applying to this type of use can be readily appreciated, while other factors cannot be evaluated accurately.

In a large series of family studies from epidemic and non-epidemic areas, made by various workers including ourselves, it appears that approximately 60% of all secondary cases have occurred by the fifth day after onset of the index case (Fig. 1). Likewise, we and others have observed that the average time between onset and diagnosis is 4 to 5 days. Thus, this 50% to 60% of all secondary cases will have become ill before the physician is in position to inject the other members of the family. If injections are performed at this time (fifth day) what can be anticipated for those cases expected to occur within the next week after injection? Our experiment appears to furnish an answer to this. Few, if any, cases with onsets within a week after injection were completely prevented, but modification of the involvement occurred to an important degree. In our series of 12 children with onset one week after injection no case had significant residual involvement; thus, modification of severity would be anticipated during this week (5 to 12 days after onset of index cases). This, I believe, is essentially as important in the long run as preventing the disease completely. Approximately 30% of all secondary cases normally occur during this period. The morbidity rate in the total family population, including adults, for this period in our series of 482 families with 2,189 exposed persons was 8.3 per 1,000 and in a slightly larger series in New York State[5] in 1950 it was even higher. Compare this to 0.46 per 1,000 in just the 1 to 6-year age group during the 4 weeks of highest incidence during the season in our Texas study.

After this time (twelfth day) only 10% of all secondary cases are expected. Most of these should be completely prevented by gamma globulin. Family rates have also been computed for this last 10% of cases (occurring more than 12 days after the onset of the index cases) but numbers are small and standard deviations large. It appears, however, that these rates (for all ages in the family) are still higher than those for all children under 15 years of age in the community, except where epidemic rates attain levels of 300 to 500 per 100,000 or greater for the total epidemic. Another important observation is that in all studies of a similar nature, in families, there is a tendency for the later secondary cases to occur among the older children or adults. Thus, it would appear wise to extend the age coverage in families to include young parents and certainly all pregnant women. But, use in family contacts of diagnosed cases may not be the most effective method, though obviously it deserves careful consideration for administrative rea-

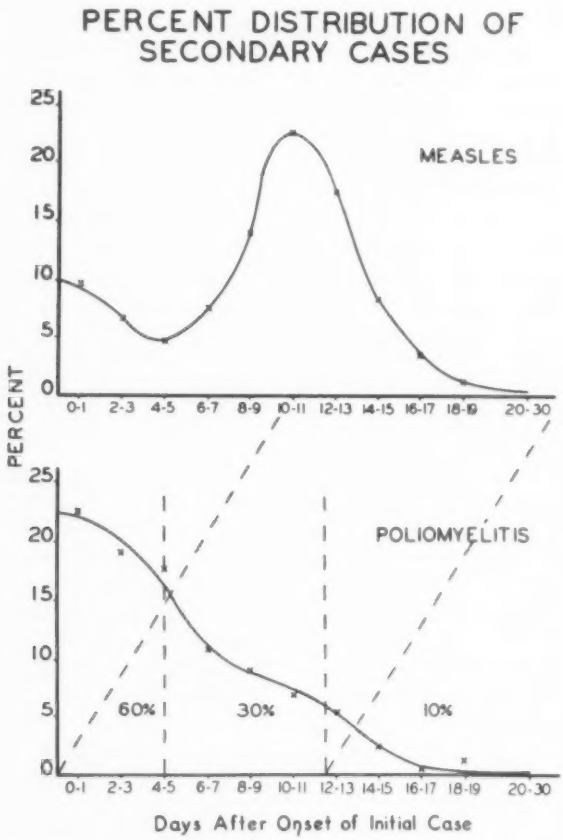


Fig. 1. — Data on measles from "Measles and Scarlet Fever in Providence, R. I., 1929-1934 with Respect to Age and Size of Family" by Edwin B. Wilson, Constance Bennett, Margaret Allen and Jane Worcester. Proc. Am. Philosophical Soc., **80**, No. 3, February, 1939.

sons and to avoid political or other public pressures. Based on the average annual number of reported cases only a portion of available stocks of gamma globulin would need to be used in this manner alone. Let us look for other possible uses.

The distribution of second cases in family groups for poliomyelitis and measles is shown in Fig. 1 by day of onset after the initial case. The reason for the difference in the shape of the two curves for percent distribution of secondary measles and poliomyelitis cases is believed to be due to failure to recognize the primary poliomyelitis infection in the family, since it, like all other infections, is much more likely to be of an abortive or inapparent type than one that can be clinically diagnosed. This would appear reasonable since only 1 of 100 or more infections with poliomyelitis virus are clinically recognized. This undiagnosed, primary infection then leads to multiple secondary infections, among which may occur one with clinical manifestations permitting diagnosis. This epidemiological concept, pointed out by Aycock and supported by much subsequent evidence, leads to what may actually be the most effective use of gamma globulin: use in the family at the time of exposure of most of the family members. When this occurs through inapparent infection it cannot be recognized, but the primary infection in the family must frequently be manifested as an undiagnosed, abortive case. Thus, we consider next the familial contacts of suspect-abortive cases.

3. Familial Contacts of Suspect-abortive Cases. The more severe a poliomyelitis epidemic becomes the higher will be the proportion of undiagnosed, febrile illnesses that are actually abortive poliomyelitis. A large number of these will represent primary poliomyelitis infections in the family. Injection of family members at this time should be prior to the onset of approximately 75% of all secondary cases, as in measles. Expecting modification in the earliest cases and prevention of most of the later ones, use in such families should give excellent results. Where a minor illness is misdiagnosed as abortive poliomyelitis there will be a waste in gamma globulin use. However, in indiscriminate mass prophylaxis of children in the same epidemic community these children in the home of a child with a minor illness not caused by poliomyelitis virus would have been inoculated together with thousands of others with no known or even suspect exposure. Another advantage of this method of use is that families with paralytic cases will be injected several days earlier if the doctor does not have to wait until he can be certain of the diagnosis, which for the unskilled may not be until gross paralysis is observed. I would not recommend the "suspect-abortive case contact" method except where high epidemic rates were recognized, for only under these circumstances would a high proportion of suspect cases actually represent abortive poliomyelitis infection. Under such circumstances, however, I believe that epidemiologic and immunologic evidence strongly supports the hypothesis that this is a more selective method of administration than indiscriminate and essentially simultaneous mass immunization of all children.

There is not enough gamma globulin for all children in all epidemic communities. Furthermore, 25 to 50 special teams with tremendous numbers of syringes and needles would be necessary almost simultaneously in late July and August to care for mass immunization in all heavily hit communities, for the procedure differs from that of the small subcutaneous injection commonly used in mass immunization. The more selective approach

to families, based on diagnosis or suspect diagnosis by a physician could be handled largely by physicians in private practice with referral of others to a health department clinic. This has much to commend it. Opponents of this method say there is no direct, experimental proof that it will work and they point out that abortive poliomyelitis cannot be accurately diagnosed. I agree entirely, but since those whom I have heard opposing this method insist on indiscriminate, mass community injection instead and claim that anything else is unjustifiable, I fail to see the logic. They would include in mass prophylaxis not only the same children wastefully injected under the suspect-case contact method because the wrong index diagnosis had been made, but also all other children in all families where not even a suspect illness occurred, and would include many families where known and suspect cases had occurred weeks before and had probably left the family solidly immune.

I feel strongly that lack of direct, experimental evidence should not restrict administrative practice from doing what epidemiologic and immunologic evidence strongly suggests is reasonable. I also appreciate keenly that we lack much of the knowledge we need and that we should seek to accumulate conclusive evidence to support the methods suggested, through follow-up and careful research planning in selected areas. But meanwhile, since we are forced to employ an immunizing agent suited for very limited use, under circumstances where a far better one is needed, let us not discard in our planning all evidence and all logic that do not meet the requirements of positive proof through controlled field demonstration.

Summary. There are serious limitations in the use of gamma globulin in poliomyelitis prophylaxis. These are due in part to the fact that this is an agent giving temporary, passive protection only. However, still more important are the difficulties presented by the disease itself; a majority of infections unrecognized, exposure unrecognized in time or place, and susceptibles indistinguishable from immunes. This leaves no alternative to shotgun use of any immunizing agent, gamma globulin or vaccine, but one should aim over a shotgun, when possible, to increase the ratio of kills per shots or pellets used.

REFERENCES

1. **Hammon, W. McD., Coriell, L. L.,** and **Stokes, J., Jr.**: J. Am. Med. Assn., **150,** 739, 1952.
2. Iidem: Ibid., **150,** 750, 1952.
3. **Hammon, W. McD., Coriell, L. L., Wehrle, P. F., Klimt, C. R.,** and **Stokes, J., Jr.**: Ibid., **150,** 757, 1952.
4. **Hammon, W. McD., Coriell, L. L., Wehrle, P. F.,** and **Stokes, J., Jr.**: Ibid., **151,** 1272, 1953.
5. **Korns, R. F.**: Unpublished data.

SARCOIDOSIS IN THE ARMED FORCES

By Robert S. Nelson, Col. M.C.
CHIEF OF MEDICAL SERVICE AND USAREUR CONSULTANT IN GASTROENTEROLOGY
(From the 98th General Hospital, Munich, Germany)

Sarcoidosis is a disease of unknown etiology and of widespread involvement of the human body. As such, it is capable of presenting a multitude of clinical appearances, and is difficult to diagnose. Many excellent descriptions of this disease and papers on every aspect have appeared in the past twenty years, and more are making their appearance. As yet, however, no causative agent has been found, despite comparisons with pathological pictures and clinical manifestations of similar diseases of known etiology. Most of these diseases are sufficiently similar in both respects to be extremely confusing, but from the large amount of evidence available there has arisen, in the minds of most, the conclusion that sarcoidosis is a clinical entity of its own. That there is much evidence for the closest relationship, that to tuberculosis, cannot be denied; it also cannot be denied that there is as much evidence pointing to the fact that the two are separate. The arguments for and against this relationship, as well as to other diseases, such as histoplasmosis, brucellosis, beryllium poisoning and leprosy, are best set forth in specific papers on this subject as well as several excellent reviews of the disease as a whole[4,6,9,13,15,16].

The clinical course is extremely variable. There are frequent exacerbations and remissions without apparent cause, confusing the results of attempts at therapy. It is easy to understand the spectacular death of a patient when sarcoidosis involves his heart muscle, but difficult to see why two patients, both with approximately the same involvement of lungs and lymph nodes, go their separate ways, one to complete remission, the other to "alveolar-capillary-block"[23] (fibrosis preventing oxygen exchange) and death. While any structure in the body may be involved, it is important to note that the sarcoid granulomas do not tend to invade the serous and mucous surfaces or periosteum of bones with erosion. Illness is prolonged and may terminate in healing, meanwhile producing few clinical symptoms. While the course is usually benign, some evidence is accumulating that sarcoidosis may be more productive of disability and death than was formerly thought[15,16].

We have been impressed with the relatively large number of proven cases of sarcoidosis diagnosed on the medical service of the 98th General Hospital, Munich, Germany. These have characteristically run the gamut of clinical manifestations and variability of activity. Impressive particularly has been the proven liver involvement, and the present study was undertaken with two objects in mind: 1) the overall characteristics of sarcoidosis in the Armed Forces, and 2) an evaluation of liver biopsy in the diagnosis. The importance of this last procedure, as well as its pitfalls, has been excellently brought out by Klatskin and Yesner[7].

Material. Cases were drawn from large numbers of patients transferred in from many areas of USAREUR (United States Army, Europe), Austria and Italy, and during an 18 months' period there were 17 cases of sarcoidosis. The ages in this group varied from 19 to 37, with an average of 26 years. White exceeded Negro patients 9 to 8. Statistics are not available on relative proportions of white and Negro troops in the source areas, and this series is too small to be sig-

nificant, but the relationship is interesting in view of the findings of Ricker and Clark in their classical review of 300 cases of sarcoidosis from the files of the Armed Forces Institute of Pathology[15]. Their statistical conclusion was that the disease occurred 17 times as often among Negro as among white males in the Army. As might be expected, their age groupings are similar to ours.

Diagnostic Criteria. It is well recognized that any clinical diagnosis of sarcoidosis must be substantiated histologically. This was accomplished in all cases. In addition, certain other confirmatory data are interesting as distinguishing between sarcoidosis and other similar diseases. Blood values in our series showed only minor variations, as did urine determinations, in agreement with other reports[9,13]. Sedimentation rates, reported in 8, showed moderate elevations in 4. Serum proteins showed alterations in 12 instances, most evidently as changes in the globulin fraction. Tuberculin (PPD) testing in 13 cases revealed the following: first and second strengths negative in 6; first strength negative and second positive in 3; both positive in 4. Bone marrows showed no abnormalities in 2 instances. Cases showing pulmonary changes suggestive of possible tuberculosis all exhibited negative sputa, gastric washings, and specific bacteria were absent in all pathological specimens investigated.

Analysis of Cases. In attempting to tabulate presenting symptoms and clinical signs it is obvious at once that the extreme variability of symptoms would make any table unusually involved. In every group of cases, there are those which stand alone in diverse and multiplied manifestations. Table 1 is an attempt to classify our group as to the most commonly seen symptoms and signs, with those cases which follow no set pattern listed separately.

TABLE 1.—SYMPTOMS AND SIGNS IN 17 CASES OF SARCOIDOSIS (GROUPED AS TO MAIN PRESENTING SYMPTOMS)

Presenting Symptoms:	*No.*	*Case No.*
1) Aching chest pain	4	1, 6, 10, 12
2) Asymptomatic, routine chest film suspicious (hilar adenopathy with or without pulmonary infiltration)	5	3, 8, 7, 15, 17
3) Swollen nodes	2	9, 13
4) Others:		
1. Chills, fever, anorexia, cough and sputum		11
2. Sore throat for months, expectoration of dark blood, no cough		4
3. Edema of ankles and legs to knees with erythematous nodular patches, swollen joints		5
4. Anorexia and fatigue, weight loss, dysuria, polydypsia, polyuria, vomiting, cough with clear sputum		2
5. Nausea and vomiting, fever, swollen painful joints, marked weight loss		14
6. Migratory arthritis with right mediastinal and hilar nodes on chest film		16

Physical Signs:	*No.*
1) Lymphadenopathy, involving all or part of system	13
2) Throat lesions	1
3) Swollen painful joints	3
4) Râles, minimal	1
5) Edema of legs with erythema	1
6) Enlargement of liver and spleen	1

The high incidence of chest pain in this series is surprising in view of the relatively slight occurrence of the symptom in other series[9,15]. No explanation can be given for this observation, although it was noted that in every instance the pain cleared soon after rest on the hospital ward was instituted. The low numbers of physical findings exclusive of the usual lymphadenop-

athy is interesting and often characteristic, especially in patients who are obviously quite ill. No case presenting uveitis, parotitis or skin involvement with typical sarcoid lesions was seen, nor was bone involvement noted despite extensive investigation. Two cases, one with pterygium (Case No. 15), and one with chronic iritis (Case No. 2), were both studied intensively by the eye department with negative results, and no other eye lesions were seen. Also of interest is the absence (with one exception, Case No. 16) of palpable enlargement of liver or spleen in any patient. In order to highlight some of the more unusual types of involvement in sarcoidosis, the following illustrative cases are presented in detail.

Case Reports. Case No. 2, a 21-year old white male, was admitted complaining of chronic eye inflammation plus anorexia for 5 months and intermittent dull pain over the lumbar region for 8 months. In addition, he had suffered 20 pounds of weight loss in 2 months, during which time he had noted burning on urination. Three weeks prior to admission he developed a polydypsia which necessitated his drinking one quart of water per hour. One week prior to admission he developed polyuria and vomiting from 2 to 4 times each night. Family history and past history were non-contributory. On physical examination, temperature, pulse and respirations were within normal limits. He appeared chronically ill and showed a right cervical adenopathy consisting of firm, non-tender glands. There was bilateral axillary adenopathy composed of pea-sized glands. Laboratory tests revealed a normal white count and hemogram, the sedimentation rate varied between 6 and 11 mm. per hr., and cardiolipin was negative. Chlorides were 500 mg. per 100 cc. and fasting blood sugar 97 mg. per 100 cc. Nonprotein nitrogen was 29, blood urea nitrogen 14 mg. per 100 cc. Cholesterol was 140 mg. per 100 cc. with 74% Esters, total proteins 7.54 gm. per 100 cc, albumin 3.71 gm., globulin 3.83 gm., alkaline phosphatase 3.7 units, calcium 11.25 mg. per 100 cc. Urine concentrated only to 1.007 specific gravity, there was a trace of albumin and culture was negative. Phenolsulphonephthalein showed 69% excretion in one hour. Films of the chest showed marked bilateral hilar adenopathy. Hands, feet, pelvis and skull were negative for any lesion. Examination showed no evidence of uveitis or changes which could be attributed to sarcoidosis. A biopsy of the left axillary node showed changes diagnostic of sarcoidosis. On pitressin medication the patient managed to concentrate his urine to 1.010 specific gravity, and on 40 units of pitressin daily the volume dropped to 3000 to 4000 cc. daily. Other symptoms remained essentially unchanged. After 22 days the patient was evacuated to the United States for possible nitrogen mustard therapy on the advice of a consultant.

Comment. This case illustrates involvement of the pituitary gland by sarcoid, an occurrence which, while relatively rare, has been reported and well documented a number of times[8,21]. It represents the most important reported involvement of the endocrine system by sarcoid, and actually is only a striking manifestation of generalized sarcoidosis.

Case No. 5, a 32-year old white male, was admitted to the hospital complaining of pains on the bottom of both feet and swelling of both legs below the knees for 7 days. On the day of admission to the hospital he developed erythematous red patches over both legs below the knees, the skin felt hot and tight and the feet were cold and sweaty. Past history and family history were non-contributory. On physical examination, the temperature was 101° F., pulse 112 and the respirations were 18. There was a 2 to 3 plus edema of ankles and lower legs to the knees, which was firm and showed pitting on pressure. Skin over the lower legs was warm and the feet cold. There were 15 to 20 ill-defined, reddish nodular and roughly circular patches over the lower legs. Several small, scattered inguinal nodes were found. Laboratory tests showed a normal differential and hemogram. The sedimentation rate varied from 11 mm. per hr. to a high of 48 mm. per hr. during hospitalization. Cardiolipin was negative, and the serum proteins showed a total of 6.15 gm. per 100 cc.; albumin 3.04 gm., globulin 3.11 gm. Cephalin cholesterol flocculation and thymol turbidity tests were within normal limits. Bromsulfalein excretion on two occasions 6 weeks apart showed normal values. The chest film showed moderate bilateral hilar adenopathy. The electrocardiogram was normal. Tubercu-

lin (PPD) revealed first strength negative, second strength 2 plus. Biopsy of the liver revealed a granulomatous process compatible with sarcoidosis. The erythema and swelling of the lower legs subsided in 7 days but ankles still swelled on walking and the feet remained cold. His fever subsided in the first week. There were no other symptoms and the patient was evacuated to the United States for further observation and treatment.

COMMENT. Inasmuch as the most striking clinical manifestation of this case is erythema nodosum of both lower extremities, it must be admitted there is some disagreement as to its occurrence in cases of sarcoid. Klatskin[7] seems to feel that erythema nodosum is a separate entity, and that the finding of characteristic granulomas in the liver, plus hilar adenopathy, still do not constitute proof of sarcoidosis. Others, notably Myers *et al.*[10], who cite 3 cases with this manifestation plus joint involvement and positive muscle biopsies, feel that it is only a symptom in sarcoid. Certainly it does occur as a manifestation in other diseases, notably tuberculosis and rheumatic fever, and Riley[16] has listed it as an authentic sign of sarcoid in a recent comprehensive review. We feel that this patient's basic disease was sarcoidosis. Unfortunately, no muscle biopsies were performed.

CASE NO. 14, a 34-year old white male, was admitted with nausea and vomiting without relation to food or time of day, malaise and a chronic weight loss of 50 pounds in one year. Vomiting occurred once or twice a week and consisted of undigested food he had eaten 6 to 8 hours previously. Shortly before admission he developed painful swollen ankles and a spiking fever up to 104° F. After several days his right knee swelled and several finger joints became painful. The joint symptoms cleared after several weeks, but the recurrent fever of 103 to 104° continued almost every day. Most of the spikes of his fever occurred about 4 a.m. and he had no afternoon or evening fever. There were no chills or severe perspiration associated. Family history and past history were non-contributory. Physical examination revealed a man weighing 158 pounds who appeared to have lost considerable weight. There was one somewhat firm node in the left axilla and no other findings of note. The laboratory tests revealed a normal differential and hemogram. The urine was negative. Agglutinations for typhoid, paratyphoid and brucella were negative. Blood cultures were negative on 5 occasions. Sputa were negative on smear and culture for acid fast bacilli and cultures were followed for 8 days. Tuberculin (PPD) first and second strengths were negative. Total serum bilirubin was 0.32 mg. per 100 cc., the one-minute serum bilirubin was 0.09 mg. per 100 cc. Cephalin cholesterol flocculation was negative, thymol turbidity 2.5 units. Total serum protein was 5.96 gm. per 100 cc.; albumin 2.31 gm., globulin 3.65 gm. Roentgenogram of the chest showed a dense, almost nodular infiltrate in the right base with a similar infiltrate in the left costophrenic angle. Both hili were prominent. Review of chest films since 1949 (2 years) showed no change up to the time of admission. Films of the hands and feet were normal. Liver biopsy revealed granulomatous lesions compatible with sarcoidosis. After the first week of hospitalization his vomiting ceased. He felt perfectly well and had no direct complaints. Fever continued in the early morning and there was a slow, progressive weight loss of 2 to 3 pounds weekly for 4 weeks. Following this the temperature returned to normal and he began to gain weight. Films of the chest remained unchanged.

COMMENT. As involvement of the gastrointestinal tract is rare in sarcoid, it is felt that the vomiting in this case was undoubtedly due to the general involvement and toxicity of his condition. Klatskin and Yesner report gastrointestinal symptoms in 11 of 15 cases of proven sarcoidosis, but could not correlate this finding with involvement of the liver. The similarity of lesions of regional enteritis to those of sarcoid is well known[22], but the relationship is in dispute, and there was no evidence here of that disease. Joint symptoms are not common, but do occur, and a recent report[10] emphasized that there is muscle involvement at these times. The rather typical remission following what appeared to be rapid progression is worthy of note,

and is the characteristic that has given sarcoid its benign reputation.

Case No. 4, a 24-year old colored single male, was admitted 6 August 1951, because of bilateral hilar enlargement seen on chest film done at time of re-enlistment, July, 1951. He had no specific complaints. Family history was non-contributory. The patient had entered the service in September, 1947, and had been in the hospital on two occasions. In May, 1948, he was admitted and discharged as somatization reaction, with vague gastrointestinal complaints and low back ache. Physical examination at this time noted bilateral inguinal adenopathy and a 1-cm. axillary node. Roentgen studies of spine and gastrointestinal tract proved negative, but no chest film was made. In January, 1949, he was admitted for repair of a right indirect inguinal hernia. Bilateral inguinal adenopathy was noted at this time, but again no chest film was taken. He had no other complaints. He had been asymptomatic since then up to the present admission. Physical examination showed normal temperature, pulse and respirations, normal blood pressure, enlargement of axillary, epitrochlear and inguinal lymph nodes, no chest signs, no evidence of liver and spleen enlargement. Laboratory studies showed slight leukopenia with moderate lymphocytosis, normal hematocrit and sedimentation rate. Bleeding, clotting and prothrombin times were within normal limits. Urine showed 35 to 40 white cells per high powered field, but was otherwise negative. Total serum proteins were 7.54 gm. per 100 cc.; albumin 4.10 gm., and globulin 3.44 gm. Total serum bilirubin was 0.26 mg. per 100 cc., one-minute serum bilirubin 0.05 mg. per 100 cc. Cephalin cholesterol flocculation was negative, and thymol turbidity 4.5 units. Bromsulphalein retention was 8.5% in one hour (5 mg. per kilogram), tuberculin (PPD) first strength negative, second strength one plus. Chest film revealed bilateral hilar adenopathy, with a probable diagnosis of sarcoidosis or lymphomatosis. A liver biopsy was performed which showed "Hepatitis, granulomatous, compatible with sarcoidosis". Course in the hospital was essentially uneventful until November, 1951, following his transfer to a general hospital in the United States, when he began to complain of fatigue, lassitude and dyspnea on exertion. Laboratory tests remained essentially the same. The spleen was found to be somewhat enlarged, but liver function tests became normal. A Kveim reaction performed 15 November 1951 gave a positive reaction for sarcoidosis, proved by biopsy. Sputum tests were negative for tubercle bacilli, first strength PPD became one plus, histoplasmin and coccidoidin skin tests were negative. Detailed pulmonary function tests were performed with essentially normal results, and due to the persistence of symptoms it was decided to try ACTH therapy. On February 19, 1952, he was started on daily intravenous injection of 20 mg. of ACTH which was continued for 14 days. On 5 March, 1952, ACTH was discontinued and cortisone begun, and this medication was continued in gradually lessening doses until 5 May 1952, at which time he had received a total of 280 mg. of ACTH and 5.35 gm. of cortisone. Subjectively the patient seemed improved, and could perform light work around the ward, but lymphadenopathy and chest film showed no changes of note. He was not deemed able to continue full duty, and was discharged to Veteran's Service care in May, 1952.

Comment. Detailed history of this patient was given because he illustrates the chronicity and unpredictability of sarcoidosis which makes it a severe disposition problem in the Armed Forces. It is impossible to determine the progression of any given patient, even those who are asymptomatic at the time of diagnosis. It is interesting that ACTH and cortisone therapy gave only slight subjective relief, despite which it was necessary to discharge him from the service as unable to perform full military duty.

Liver Biopsy. Typical hepatic granulomas have been found in the active stage of sarcoidosis with rather remarkable frequency. The most prominent of these studies, and one which has served to focus attention on the procedure as importantly diagnostic, is that by Klatskin and Yesner[7]. Others have reported similar results in smaller series. Although the dangers of biopsy have been pointed out by many, these authors report 650 procedures without serious accidents, and we have in this hospital performed 500 liver biopsies without major complications. Sixteen needle biopsies, using the Vim-Silver-

man needle as modified by Voegtlin and Nelson[11] and the trans-thoracic approach, were done in the 17 cases reported here, 11 exhibiting more or less typical granulomas. The two cases (No. 2, 9) not biopsied showed typ-

estingly, and in contrast to other series[9,13] only one of our cases had enlarged liver and spleen on physical examination. Liver function tests as compared to results of biopsy are given in Table 2.

TABLE 2.—SIGNIFICANT DATA IN 15 CASES OF SARCOIDOSIS WITH LIVER BIOPSY

Patient Number	*Total Serum Bilirubin* / *1' Serum Bilirubin*	*Cephalin Flocculation*	*Thymol Turbidity*	*Bromsulfalein Retention* %	*Tot. Protein* / *Alb., Glob.*	*Biopsy*
12	0.42 0.04	Plus–Trace	3.5–5.25	9.0	6.89 3.37, 3.52	Pos.
5	0.34 0.08	0	2.5	6.0 4.0	6.15 3.04, 3.11	Pos.
6	0.52 0.05	0	5.0	6.5 5.0 4.0	6.52 3.46, 3.06	Pos.
11	0.34 0.07	0–Plus– 2 Plus	4.0–5.0 6.0	22.0 28.0	7.18 2.59, 4.59	1st Neg. 2nd Pos.
4	0.42 0.07	0	1.25	3.0	6.19 3.33, 2.86	Neg.
10	0.36 0.10	0	1.50	5.0	7.23 2.96, 4.27	Pos.
14	0.32 0.09	0	2.5	9.5	5.96 2.31, 3.65	Pos.
3	0.66 0.09	2 Plus– 2 Plus	7.8–8.5	9.0 11.0	6.79 2.59, 4.20	Neg.
8	0.26 0.05	0	4.5	8.5	7.54 4.10, 3.44	Pos.
7	0.34 0.05	0	2.25–1.0	2.5	6.05 4.10, 1.95	Pos.
1	0.50 0.11	2 Plus	15.0	10.0	7.09 4.39, 2.70	Pos.
13	0.32 0.10	0	8.5	3.5	7.18 4.10, 3.08	Neg.
15	Normal	0	Normal	Normal	6.05 3.46, 2.59	Neg.
16	0.62 0.10	0	6.5	8.5	7.49 3.71, 3.78	Pos.
17	0.48 0.05	0	6.25	5.5	8.20 3.59, 4.61	Pos.

ical lymph node changes on pathological examination and clinical pictures compatible with generalized sarcoidosis. In 6 of 11 positive cases, lymph nodes obtained surgically showed nonspecific changes. Furthermore, 6 (Cases No. 1, 3, 7, 8, 12, 17) showed no clinical evidence of activity. Inter-

Changes in cephalin cholesterol flocculation with or without changes in thymol turbidity occurred in 4. Biopsy was positive in 3 of these, negative in one (Case No. 3) in which the bromsulphalein (BSP) retention was also slightly elevated. Bromsulphalein retention was positive in 7, in 6 of which

the biopsy was positive. It is interesting to note that in Case 11, in which the BSP finally rose to a total of 28%, the first biopsy was negative, and the second, taken one month later, showed typical granulomas. Possibly a second specimen from Case 3 might have given similar results.

With one or more liver function tests positive, 6 biopsies were also positive. With all tests negative, 5 biopsies were positive. In 4 negative biopsies function tests were altered in one, negative in 3. Thus, while there is no definite correlation, altered liver function, and especially BSP retention, would seem worthy of close attention. With an initial negative biopsy, if tests continue altered or if BSP retention rises to higher levels, a second biopsy would seem to be in order, as suggested by Case 11. Certainly all cases showing clinical activity should be biopsied, and negative function tests, clinical inactivity or lack of hepatomegaly should be no deterrent.

Treatment. Therapy in sarcoidosis has been unsatisfactory. Arsenic, ultraviolet, Roentgen-ray, radium, tuberculin, antileprol, calciferol, nitrogen mustard and the antibiotics have been used without effect. Recently ACTH and cortisone have come to the fore as showing definite improvement in some forms of the disease. A recent report by Siltzbach[17] in 13 patients with mixed involvement emphasizes that objective and subjective improvement in a varying degree may be expected in all patients, and that fresh lesions appear to be more responsive than old ones. Of 10 patients in whom therapy was terminated, 7 relapsed. It would appear that these agents are not a definite cure for all types of involvement with sarcoid, but certainly they are the most promising in producing remission and amelioration of symptoms. No definite therapy was attempted before transfer in our cases, as it was felt that such measures should be begun where they could be carried to their logical conclusion over a long period of time. In retrospect, several of those with acute symptoms might well have been tried on ACTH or cortisone prior to evacuation to the Zone of the Interior.

Discussion. Sarcoidosis is recognized as a generalized reaction to some unknown stimulus. The complicating factor of many known stimuli showing the same pathological response makes its diagnosis complex. Its variability of course and poor response to most therapeutic agents cloud its prognosis and treatment. In our series, taken from a group considered representative of the Armed Forces generally, white patients outnumbered Negroes, and there was no evidence of uveoparotid, skin or bone involvement. Since this is a rather frequently-examined group, it would appear that these types of manifestation may be later in development than those listed here. Involvement of the liver, found in necropsy material in 63 to 82%, and demonstrated by biopsy in 75% (as shown in Klatskin and Yesner's report), and in 73% of our cases biopsied, makes investigation of this organ of great importance in any attempt to establish a diagnosis in suspected cases. Involvement cannot be determined clinically on history and physical examination, since there may be no symptoms referable to the organ, and no enlargement or tenderness, although biopsy may show marked involvement. Initially available lymphoid tissue may be negative for any lesion, although the liver is affected. Evidence of sarcoidosis by liver needle biopsy probably is representative[7], and is a relatively harmless means of approach. Liver function tests show rather poor coordination with positive biopsy results, although persistently abnormal laboratory evidence should be followed

by repeated biopsies, especially if there is a consistently positive and rising bromsulphalein retention.

Summary. 1. Seventeen cases of sarcoidosis occurring in members of the Armed Forces in the European Command are reviewed. In this series white patients outnumbered Negroes, and there was an absence of uveo-parotid, skin and bone involvement in a group of rather frequently examined individuals.

2. In 15 cases biopsied, the liver yielded positive findings in 11, which again emphasizes the frequent early involvement of this organ. Correlation of clinical and laboratory evidence with results of liver biopsy are discussed, as well as the value of repeated biopsies in diagnosis.

REFERENCES

1. **Fisher, A. M.,** and **Davis, B. D.**: Bull. Johns Hopkins Hosp., **71**, 364, 1942.
2. **Galdston, M., Weisenfeld, S., Benjamin, B.,** and **Rosenbluth, M. B.**: Am. J. Med., **10**, 166, 1951.
3. **Gendel, B. R., Young, J. M.,** and **Greiner, D. J.**: Ibid., **12**, 205, 1952.
4. **Goeckerman, W. H.**: Arch. Dermat. and Syph., **18**, 237, 1928.
5. **Harrell, G. T.,** and **Fisher, S.**: J. Clin. Invest., **18**, 687, 1939.
6. **Hunter, F. T.**: New Eng. J. Med., **214**, 346, 1936.
7. **Klatskin, G.,** and **Yesner, R.**: Yale J. Biol. and Med., **23**, 207, 1950.
8. **Kraus, E. J.**: J. Lab. & Clin. Med., **28**, 140, 1942-43.
9. **Longcope, W. T.,** and **Freiman, D. G.**: Medicine, **31**, 1, 1952.
10. **Myers, G. B., Gottlieb, A. M., Mattman, P. E., Eckley, G. M.,** and **Chason, J. L.**: Am. J. Med., **12**, 161, 1952.
11. **Nelson, R. S.**: Gastroenterology, **21**, 289, 1952.
12. **Nelson, C. T.**: J. Invest. Dermat., **10**, 15, 1948.
13. **Reisner, D.**: Am. Rev. Tuber., **49**, 289, 437, 1944.
14. **Renold, A. E., Forsham, P. H., Maisterrena, J.,** and **Thorn, G. W.**: New Eng. J. Med., **244**, 796, 1951.
15. **Ricker, W.,** and **Clark, M.**: Am. J. Clin. Path., **19**, 725, 1949.
16. **Riley, E. A.**: Am. Rev. Tuberc., **62**, 231, 1950.
17. **Siltzbach, L. E.**: Am. J. Med., **12**, 139, 1952.
18. **Sones, M., Israel, H. L., Dratman, M. B.,** and **Frank, J. H.**: New Eng. J. Med., **244**, 209, 1951.
19. **Stuart, B. M.**: Am. J. Med. Sci., **208**, 717, 1944.
20. **Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Roche, M., Staehelin, D.,** and **Wilson, D. L.**: New Eng. J. Med., **242**, 783, 824, 865, 1950.
21. **Tillgren, J.**: Brit. J. Dermat. and Syph., **47**, 223, 1935.
22. **Watson, C. J., Rigler, L. G., Wangensteen, O. H.,** and **McCartney, J. S.**: Gastroenterology, **4**, 30, 1945.
23. **West, J. R., McClement, J. H., Carroll, D., Bliss, H. A., Kuchner, M., Richards, D. W.,** and **Cournand, A.**: Am. J. Med., **10**, 156, 1951.

HYALURONIDASE AND THE SUBCUTANEOUS ADMINISTRATION OF ELECTROLYTE-FREE GLUCOSE SOLUTION

By F. M. Mateer, M.D.*
ASSISTANT PROFESSOR OF RESEARCH MEDICINE

K. L. Garver, M.D.
FELLOW IN RESEARCH MEDICINE

M. J. Sakol, M.D.
TEACHING FELLOW IN MEDICINE

AND

T. S. Danowski, M.D.
PROFESSOR OF RESEARCH MEDICINE

(From the Department of Research Medicine and the Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania)

Hyaluronidase is widely employed to facilitate the subcutaneous administration of electrolyte and non-electrolyte containing fluid[2,7-10,12]. With respect to the latter it has been amply demonstrated that the rapid administration of large volumes of electrolyte-free fluid by hypodermoclysis can produce hypochloremia, hemoconcentration, and impairment of circulatory efficiency. Studies in dogs and in man indicate that these changes result from a diffusion of extracellular electrolytes into the injection site. Such segregation of solutes in the hypodermoclysis pool lowers concentrations in the remainder of the extracellular space. Water then moves into cells, and the volume of extracellular fluid, and of plasma in particular, becomes reduced. With changes of sufficient magnitude the circulation time is prolonged, the venous return and cardiac output decline and the blood pressure falls[1,4,15]. This sequence of events is not observed with solutions which approximate extracellular fluid in their sodium and chloride content.

It has been suggested that hyaluronidase intensifies the changes induced by salt-free hypodermoclysis[1,6]. The studies herein presented describe the hemostatic and hemodynamic changes which occurred when electrolyte-free solutions were administered subcutaneously with and without hyaluronidase.

Method. Eleven diabetic children weighing from 30.0 to 64.1 kilograms were given an aqueous solution of 5% dextrose subcutaneously in dosage of 18.9 to 52.4 cc. per kg. of body weight. Two injection sites in each thigh were used. Hyaluronidase** was injected initially and during the course of the procedure in amounts of 300 to 1200 turbidity reducing units. In 9 of these subjects, an attempt was made to give the same amount of glucose solution at comparable rates without hyaluronidase.

In all instances the subjects were fasting but had received their usual insulin dosage. They remained recumbent throughout the procedure. Initially, at the completion of the infusion, and approximately 2 hours later the pulse rate, blood pressure, ballistocardiogram, and arm-to-tongue circulation time were obtained. The body weight was then determined after voluntary voiding in the upright position. Blood samples were

* At present a Research Fellow of the American Heart Association.

** "Wydase" kindly supplied by Wyeth Laboratories.

withdrawn at these same times for hemoglobin, non-protein nitrogen, glucose levels as well as for serum carbon dioxide content, chloride, sodium and potassium analyses[3,4]. The cardiac output was estimated according to the modification of Tanner from tracings made with a Starr high frequency ballistocardiograph[13,14].

Results. The data in Table 1 based on hypodermoclysis experiments without and with hyaluronidase, respectively, indicate that the concomitant use of the enzyme increased the rate of administration in 6 of the 9 studies in which comparisons were made in the same patient. In L.W. equally high rates of flow, 1000 cc. per hour, were present in both the control and hyaluronidase experiments. In L.B. and R.W. the hypodermoclysis entered the subcutaneous spaces at somewhat slower rates even though the enzyme was used. In addition, it should be noted that in G.P., J.R., and W.W. intense discomfort made it impossible to administer, during the control hypodermoclysis, the same volumes of glucose solution used in the hyaluronidase studies.

TABLE 1.—SUBCUTANEOUS ADMINISTRATION OF 5% GLUCOSE IN WATER WITH AND WITHOUT HYALURONIDASE

				5% Glucose in H_2O		
Subject	*Body Weight (kg.)*	*Time (hrs.)*	*Hyaluronidase (units)*	*(cc.)*	*(cc./K.)*	*(cc./hr.)*
L. W.	64.1	0–2.0	1200	2000	31.2	1000
	64.1	0–2.0	none	2000	31.2	1000
G. P.	41.0	0–1.2	450	1250	30.5	1042
	40.3	0–1.8	none	1000	30.6	556
R. S.	30.0	0–1.7	900	1000	33.3	588
	30.3	0–2.6	none	1000	33.0	385
D. Mc.	52.8	0–1.6	300	1000	18.9	625
	52.9	0–3.9	none	1000	18.9	256
L. B.	49.2	0–3.3	300	1000	20.3	303
	48.4	0–2.8	none	1000	20.7	357
J. R.	38.2	0–2.0	1200	2000	52.4	1000
	38.0	0–4.1	none	1720	45.3	420
R. B.	33.8	0–1.5	1000	1000	29.5	667
	34.0	0–1.7	none	1000	29.4	588
W. W.	51.0	0–1.8	1200	2000	39.2	1111
	51.0	0–3.0	none	1050	20.6	350
R. W.	55.6	0–2.7	1000	2000	36.0	741
	56.2	0–2.0	none	2000	35.6	1000
L. S.	43.6	0–1.9	600	2000	45.8	1053
R. M.	30.4	0–3.2	600	1000	32.8	312

Following infusion in both groups of experiments, the hemoglobin was usually found to be elevated above pretreatment levels. This did not occur, however, in 2 experiments in each of the 2 series (L.B., R.M., L.B., W.W.). In 3 of these the volume of the hypodermoclysis was low, approximating 20 cc. per kg.

From Table 2 it is evident that hypodermoclyses given with or without the enzyme usually produced hypochloremia without statistically significant change in the levels of sodium, potassium, and bicarbonate. Furthermore, the degree of hypochloremia which appeared both with and without hyaluronidase was of the same order of magnitude ("p" values ranged between 0.27 and 0.90).

Finally, it is apparent from Table 3 that the hemoglobin level, pulse rate, systolic and diastolic blood pressure, the circulation time, the rate of urine flow as well as the ballistocardiographic cardiac output were quite comparable at the time of the first and second observations following the

TABLE 2.—SERUM ELECTROLYTE CONCENTRATIONS PRIOR TO AND AFTER SUBCUTANEOUS ADMINISTRATION OF 5% GLUCOSE SOLUTION IN WATER WITH AND WITHOUT HYALURONIDASE

		With Hyaluronidase Serum (*mEq./L.*)				*Without Hyaluronidase* Serum (*mEq./L.*)			
		CO_2	*Cl*	*Na*	*K*	*CO_2*	*Cl*	*Na*	*K*
Before Hypodermoclysis		23.6±2.5 (11)	99.0±4.0 (11)	138.3±4.2 (9)	4.5±0.4 (9)	25.0±1.4 (9)	99.3±3.8 (9)	139.9±4.5 (8)	4.5±0.5 (9)
After Hypodermoclysis	*a*)	22.7±1.5 (11)	94.1*±4.7 (11)	136.0±2.6 (8)	4.5±0.7 (8)	24.3±1.6 (9)	96.7±4.3 (9)	138.2±5.8 (7)	4.4±0.3 (8)
	b)	24.0±2.2 (11)	94.3*±4.8 (11)	134.7±6.0 (7)	4.6±0.8 (8)	24.6±1.2 (8)	95.4*±3.3 (9)	138.2±6.8 (7)	4.5±0.8 (8)

"*a*" refers to observations obtained shortly after completion of infusion; "*b*" identifies data obtained 1.6 to 2.5 hours later.
* Deviation from mean of control period in each category is statistically significant.

TABLE 3.—CIRCULATORY CHANGES FOLLOWING SUBCUTANEOUS HYPODERMOCLYSIS WITH AND WITHOUT HYALURONIDASE

Hyaluronidase units		*Blood Hb gm./100 cc.*	*Change in* *Pulse rate/min.*	*Circ. Time seconds*	*Syst. Bl. P. mm. Hg*	*Diast. Bl. P. mm. Hg*	*Cardiac Output L./min.*	*Urine Volume cc./hr.*
300–1200*	*a*)	+0.5±0.9 (11)	−4±8 (11)	+1.3±2.8 (6)	−5±14 (10)	+12±14 (10)	+0.2±1.6 (11)	156±106 (11)
	b)	+1.0±1.2 (11)	+3±12 (11)	+1.4±2.3 (6)	−7±15 (11)	+12±15 (11)	+0.7±1.8 (11)	*a*) + *b*)
none*	*a*)	+0.6±0.9 (8)	−4±5 (9)	+0.8±1.8 (6)	+3±6 (9)	+12±6 (9)	−0.8±0.8 (9)	131±54 (9)
	b)	+1.4±1.2 (8)	+1±8 (9)	+1.0±1.4 (6)	+1±8 (9)	+8±5 (9)	−0.1±0.9 (7)	*a*) + *b*)

* No statistically significant difference present in any of the comparisons in these 2 categories.
"*a*" refers to observations obtained shortly after completion of infusion; "*b*" identifies data obtained 1.6 to 2.5 hours later.

hypodermoclysis irrespective of whether or not the enzyme was employed.

Discussion. There is no evidence in these studies that hyaluronidase in amounts in ordinary clinical usage discernibly modified the biochemical and circulatory changes which accompany hypodermoclysis of an electrolyte-free aqueous solution of 5% glucose. This finding is in keeping with the demonstrated safety of combined use of hyaluronidase and hypodermoclysis irrespective of the solution employed. Nonetheless, the general principle still applies: segregation of extracellular electrolytes in subcutaneous tissues as a consequence of saline-free hypodermoclysis produces biochemical alterations which may lead to circulatory collapse. The latter can be avoided by limiting the volume and the rate of electrolyte-free fluid administration via the subcutaneous route, particularly in patients with pre-existent sodium and chloride depletion[3,5,11], or by using electrolyte solutions which approximate extracellular fluid in composition.

Summary and Conclusion. The administration of hyaluronidase with volumes of fluid in ordinary clinical use did not intensify the biochemical changes and circulatory changes which accompany subcutaneous pooling of saline-free solutions. Nonetheless the knowledge that subcutaneous administration of saline-free fluids with or without hyaluronidase always results in the segregation of some extracellular electrolyte, necessitates due caution particularly in patients in whom depletion may already be present.

REFERENCES

1. **Abbott, W. E., Levey, S., Foreman, R. C., Krieger, H.,** and **Holden, W. D.**: Surg., **32**, 305, 1952.
2. **Burket, L. C.,** and **Gyorgy, P.**: Pediat., **3**, 56, 1949.
3. **Danowski, T. S., Peters, J. H., Rathbun, J. C., Quashnock, J. M.,** and **Greenman, L.**: J. Clin. Invest., **28**, 1, 1949.
4. **Danowski, T. S., Winkler, A. W.,** and **Elkinton, J. R.**: Ibid., **26**, 887, 1947.
5. **Darrow, D. C.**: J. Pediat., **28**, 515, 1946.
6. Editorial: Hyaluronidase and Hypodermoclysis., J. Am. Med. Assn., **151**, 644, 1953.
7. **Gaisford, W.,** and **Evans, D. G.**: Lancet, **2**, 505, 1949.
8. **Hallman, N., Kulonen, E.,** and **Forsander, O.**: Acta paediat., **39**, 94, 1950.
9. **Hechter, O., Dopkeen, S. K.,** and **Yudell, M. H.**: J. Pediat., **30**, 645, 1947.
10. **Jaworski, A. A.,** and **Farley, J. E., Jr.**: Am. J. Dis. Child., **79**, 59, 1950.
11. **Mateer, F. M., Greenman, L., Austin, A. C., Peters, J. H., Mermelstein, H., Weigand, F.,** and **Danowski, T. S.**: Am. J. Med. Sci., **221**, 21, 1951.
12. **Schwartzman, J.**: J. Pediat., **34**, 559, 1949.
13. **Starr, I., Rawson, A. J., Schroeder, H. A.,** and **Joseph, N. R.**: Am. J. Physiol., **127**, 1, 1939.
14. **Tanner, J. M.**: J. Clin. Invest., **28**, 567, 1949.
15. **Webb, W. R., Lemmer, R. A.,** and **Elman, R.**: Surg., Gynec. & Obst., **91**, 265, 1950.

THE MEDICAL ASPECTS OF ELECTRIC SHOCK THERAPY* (INCLUDING A STUDY OF 192 PATIENTS)

By EDMOND H. NIESEN, JR., M.D.
FORMERLY, ASSISTANT TO THE CHIEF OF THE MEDICAL SERVICE, V. A. HOSPITAL, LOUISVILLE, KENTUCKY

AND

INSTRUCTOR IN MEDICINE, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE
CINCINNATI, OHIO

(From the Medical and Neuropsychiatric Services of the Veterans Administration Hospital, Louisville, Kentucky, and from the Medical and Neuropsychiatric Departments of the University of Louisville Medical School.)

AT the First International Meeting on Modern Treatment of Schizophrenia, held in Switzerland in 1937, Cerletti and Beni[25] first reported the electric current as a convulsive stimulus in the therapy of psychotic patients. Since that time electric shock therapy (EST) has been used extensively and has largely replaced other methods of convulsive treatment.

It is the purpose of this paper to review the literature concerning the medical aspects of electric shock therapy and to present medical data relative to 192 patients who received 210 series of EST at the Veterans Administration Hospital, Louisville, Kentucky.

EFFECTS ON THE ELECTROCARDIOGRAM. Bellet *et al.*[14] studied electrocardiographic alterations during 100 convulsive treatments in 50 patients. Changes included sinus arrhythmia, sinus bradycardia, sino-auricular heart block, AV nodal rhythm, shifting pacemaker and auricular extrasystoles. They found an increase in cardiac rate lasting one to two minutes, and then a slowing of the rate which was considered to be vagal in origin and which was abolished by atropine in 3 instances. Slight changes in T and S-T segments in lead 2 were observed. In 2 instances inverted T waves in leads 1 and 2 were seen. Kline and Fetterman[29], in 1942, studied 42 psychotic patients under treatment. An acceleration in cardiac rate was seen in nearly all instances. Cardiac arrhythmias were not conspicuous. Some change in rhythm was noted in 15, but in only 2 instances was the arrhythmia of a gross nature and all rhythms returned to normal within a 5-minute period. The arrhythmias consisted of changes in the location of the pacemaker, atrioventricular rhythm, and various types of extrasystoles. An increase in amplitude in the T waves was encountered in nearly all cases.

Heitmancik *et al.*[21] made an analysis of electrocardiographic changes following 304 electrically induced major convulsions and 23 minor convulsions in 126 curarized patients. They found various disturbances of rhythm following treatment which included all types of ectopic beats, wandering pacemaker, nodal rhythm, transient SA standstill, blocked SA impulses, prolonged PR interval, Wenckebach phenomena, 2 to 1 AV block, paroxysmal auricular tachycardia, auricular fibrillation, idioven-

* Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

tricular rhythm and ventricular tachycardia. Many of the tracings showed more than one rhythm disturbance. An increased incidence of these rhythm disturbances was found in patients with organic heart disease. The authors felt that a post-convulsive increase in vagal tone was probably the mechanism involved, although a local irritability of the myocardium due to anoxia and increased work might be an additional factor. Elevation of T waves occasionally occurred so that post-treatment tracings appeared considerably improved in abnormal tracings. The authors felt that acidosis following convulsion, or a release of potassium from injured muscle cells might be responsible for this phenomena.

Plice and Pfister[35] studied 50 psychiatric patients before and after electric shock treatments. They pointed out that electrographic changes may be produced by extra-cardiac causes as well as cardiac causes, and that changes in the T waves and S-T segments can be produced by avitaminosis[27], position[41], emotions[30,31], and exercise[12]. They found that 85.7% of the pre-treatment electrocardiograms which were abnormal showed marked improvement after successful treatment. They explained that the abnormalities may have been related to the patient's emotional state. The authors stated that, as a result of their experience, it is their practice that no patient be denied treatment on the basis of T wave changes.

Effect on Blood Pressure. Igersheimer and Stevenson[22] recently studied the effect of electric shock on the blood pressure of psychotic patients. They found that immediately following the stimulus there was a sharp systolic hypertension and a lability of the diastolic pressure. Both pressures returned to pre-treatment levels within 10 to 20 minutes. They found that there was a delayed effect on blood pressure produced in normotensive patients. After 6 or 7 treatments had been given, a systolic and diastolic hypotension was present due to a progressive loss of vasomotor tonus. Following this, both systolic and diastolic pressures tended to return to pre-treatment levels within 2 weeks after the last treatment. During this delayed phase a widely divergent range of basal blood pressures was seen. Similar but more pronounced effects were found in 5 hypertensive psychotic patients.

Effect on Plasma Volume and Extracellular Fluid. Altschule and Cline[6] studied the plasma volume during electrically induced convulsions. Decreases in the plasma volume were appreciable, and varied with the severity of seizures induced. The decreases were transitory. A satisfactory explanation of this occurrence could not be given.

Altschule *et al.*[5] studied extracellular fluid and plasma volumes in depressed patients given electric shock therapy. It has long been known that depressed patients gain weight rapidly preceding the onset of a spontaneous remission. This same weight gain usually occurs in patients who improve with EST. Twelve depressed patients were studied. The extracelluar fluid volume was found to be below normal. Extracellular fluid volume was found to increase with the weight gain. Small amounts of weight gain produced no difference between extracellular water gain and increased body weight, but with a larger weight gain the extracellular water gain was not enough to account for the increased body weight. Plasma volume showed insignificant changes in the same direction as extracellular fluid volume. The authors concluded that these findings are consistent with the effects of some steroid hormones.

EFFECT ON PLASMA PROTEIN LEVEL. Altschule *et al.*[7] studied plasma protein level associated with rapid gain in weight during EST. A transitory decrease in plasma protein level accompanied the gain in weight which occurs before clinical improvement in patients getting EST. Correction of dehydration accounted for only part of this change. These studies suggested a transitory loss of protein from the circulation such as that which occurs in patients who, after a period of depletion, begin to store tissue protein.

EFFECT ON WATER METABOLISM. Altschule and Tillotson[10], in 1949, studied the effect of electroconvulsive therapy on the water metabolism in psychotic patients. They state that during each seizure plasma leaves the circulation and the hematocrit increases. These changes vary with the intensity of the convulsion. The changes last less than one-half hour. They also studied the diuretic response to ingestion of water in psychotic patients before and after EST. They found that acceleration of diuresis occurs in patients who gain weight in the course of treatment. They state that the findings resemble the effects of some steroid hormones and tentatively may be interpreted as evidence that the treatment increases the secretion of these hormones. They state further that, in depressed patients, increases in extracellular fluid volume occur when weight is gained rapidly after several treatments. The blood sodium is unchanged. This indicates that both salt and water are being retained. These results they say indicate that steroid hormones with ketone configuration at carbon 3 are active. In patients who did not receive shock treatment, steroid hormones resulted in no clinical improvement but caused salt and water retention. These patients later showed clinical improvement on EST. The authors conclude that this phenomenon is only a side reaction but that other effects of steroid hormones may be responsible for some of the clinical improvement after shock therapy.

EFFECT ON URINARY URIC ACID-CREATININE RATIO. In 1949, Altschule, Altschule and Tillotson[4] studied the changes in the urinary uric acid-creatinine ratio after EST treatment. They found that the urinary uric acid excretion is increased after treatment, with a maximum response 4 hours after the administration of EST. Creatinine excretion also increases, but this is most marked during the first 2 hours after treatment. The ratio, therefore, remains unchanged at first and then rises to a level above the control. The authors state that the conditions are different from those encountered by Thorn and Forsham and their associates[39,40] when they proposed that changes in the urinary uric acid-creatinine ratio after ACTH injection could be used as a test of adrenal cortical function. The authors felt that the interpretation of their findings was difficult, but that the change in the ratio was large enough, together with the decrease in the number of lymphocytes and eosinophils, to constitute evidence of the increased production of 11-oxysteroids after EST convulsions in man.

EFFECT ON LYMPHOCYTES AND LEUKOCYTES. In 1948, Stern *et al.*[37] found that in almost all cases a leukocytosis and lymphocytosis occurred after EST, with return to normal within an hour. The type of response was apparently not dependent on any change of the psychiatric condition in the patient, but, at least in part, due to the mechanical effect of muscular contraction.

EFFECT ON THE EOSINOPHIL COUNT. In 1949, Altschule, Parkhurst and Tillotson[8] studied the eosinophil count of 21 patients who were getting electric convulsive therapy. They found that

irrespective of diagnosis, duration of disease, or response to treatment, decreases in the blood eosinophilic cell count were found. The changes are less marked when treatments are given frequently and may return to former levels after a rest period of more than 10 days. The effect of ACTH was compared with that of shock therapy in one instance. Both were given over a period of several weeks. The hormone caused a great drop in eosinophil count, but no improvement in symptomatology, whereas convulsions caused a lesser cell response but a remission of symptoms. The authors concluded that increase in production of 11-oxysteroids, considered responsible for the drop in eosinophil cell count, is not the cause of remission in patients given EST.

Effects on the Kidney. Clute and Fitzgerald[15], in 1948, reported the first case of fatal anuria following EST. Necropsy revealed changes in the kidney closely resembling those found in the crush syndrome. Goodman[18], in 1950, reported 2 fatal cases of lower nephron nephrosis following EST. He felt that temporary changes, due to EST and resulting in vasoconstriction caused urinary abnormalities in the majority of patients. He felt that infection may be a factor, or part of a group of factors, producing progressive renal insufficiency, set in operation by the electric stimulus. Diarrhea preceded renal shutdown in both cases and could be a danger signal.

Effects on the Central Nervous System. Kaldeck[23], in 1948, reported a case of transient hemiplegia of several days' duration following EST in a physically normal young woman with psychosis. The explanation offered was vascular spasm causing structural changes in the motor pathways in one side of the brain. The author felt that cerebral vasoconstriction occurs in nearly all cases of EST, the hemiplegia, appearing because the spasm occurred within the motor pathways. In 1948, Karliner[26] published a review of neurologic signs and complications of EST. He cited the work of Alpers and Hughes[2] experimenting with cats, and Hilbrunn and Weil[20] with rabbits, which described petechial hemorrhages in the meninges of the brain and spinal cord, and within the brain, brain stem and spinal cord. The hemorrhages apparently resulted from ruptures of small veins and capillaries. No proliferative glial reaction was seen. Changes occurred after even one shock treatment and were associated with edema of the surrounding tissue. Dosages of current were high, however. He cited the work of Newburger, Whitehead, Rutledge, and Ebaugh[33] who found reversible changes of the nerve cells in the brains of dogs following EST. Karliner also pointed out other experiments with cats by Alexander and Lowenback[1], and with Rhesus monkeys by Winkelman and Moore[44] and by Barrera, Lewis, Pacella and Kalinowsky[13]. Changes were found only in the path of the current and were, for the most part, minimal. No hemorrhages were seen. There were some changes in the nerve cells but these were seen both in control and experimental animals. These investigators concluded that temporary biochemical or physiological changes, rather than permanent central nervous system changes, were brought about by the passage of the electric current. Karliner felt that animal experiments are not conclusive with regard to human beings. He stated that in most cases, where human brains have been examined following EST, complicating factors were present and no valid conclusions could be drawn. He felt that no permanent damage results to the central nervous system in patients who undergo these treatments, provided they are properly selected.

Riese and Fultz[36], in 1949, reported a case of flaccid paralysis, hallucinations and sudden death following EST. Histologic examinations of the central nervous system showed fatty products in the nerve cells, cellular changes and glial reactions, scattered areas of disruptions and explosive destruction, rents and slits associated with displacement of the ganglion cells. It was concluded that the changes were not specific, but that they are important because of their combined and otherwise unexplainable appearance in a patient submitted to electric shock which was followed by sudden death.

Electric Shock Therapy on Patients Considered Bad Risks. Moore[32] states that when electric shock convulsive treatment was first used, patients were refused treatment because of cardiovascular disease, acute infections, tuberculosis or other lung disorders, thyrotoxicosis, intracranial disorders, central nervous system diseases, and hypertension. Since that time patients with many of these complications have been treated successfully. He reported only 2 deaths in over 2000 cases (20,645 convulsive treatments), of whom 238 had heart disease. In 190 patients with hypertension no ill effects were observed and in some cases improvement in the hypertension was found. Straker[38] has treated successfully a patient who had hemiplegia and aphasia of 2-years' duration.

Kleinschmidt *et al.*[28], in 1949, reported on 825 patients treated with electric shock or Metrazol. They had 4 fatalities. The first death was attributed to respiratory paralysis caused by curare; the second case had hypertension and coronary artery disease and sustained a myocardial infarct after his 16th EST; the third was a hypertensive who developed an anterior wall infarction 6 weeks after his last EST treatment; and the fourth was a patient who committed suicide after his first treatment. In their series, a patient with bilateral active pulmonary tuberculosis was successfully treated. A 75-year old man with complete heart block, idioventricular rhythm, and intraventricular conduction disturbances was successfully treated. A 42-year old woman with mitral stenosis was successfully treated, as was a case with an old anterior wall infarction. Forty-four patients in the old age group were treated successfully.

Contraindications to Electric Shock Therapy. Williams and Barrera[43], in 1950, evaluated the contraindications to electro-convulsive treatment with a review of the literature and their own experiences with 14,000 individual treatments during a two and one-half year period. They concluded that definite contraindications are congestive heart failure, recent myocardial infarction, and aneurysm of the aorta. They felt that there is a significant risk in making the patient's physical condition worse in recent cerebral vascular accidents, acute respiratory infections and active peripheral vascular disease. They stress that in each case the psychiatric indications for treatment must be weighed against co-existing disorders which might increase the risk of treatment.

Although myocardial infarction has been considered a contraindication to treatment, Hejtmancik *et al.*[21] state that Harris treated an acute suicidal patient who had an acute myocardial infarction and the patient survived the treatment.

Pregnancy apparently does not constitute a contraindication, although this is a controversial point. Doan and Houston[16] reported 7 cases of EST during pregnancy. Curare was given to moderate the convulsions. In all cases the pregnancy was not complicated by the treatment and an uneventful delivery was performed at term.

DEATHS FOLLOWING ELECTRIC SHOCK THERAPY. In 1948, Will, Rehfeldt, and Newman[42] summarized 33 deaths that they had collected in the American and English Literature. They found that the majority of patients were over 40 years of age. In 16 cases in which the information was available, death occurred in less than 9 treatments. Of the 33 deaths, 26 were apparently related to shock therapy. Curare had been used in only 4. Twelve died of cardiac failure, 2 of respiratory or cardiac failure, 2 in status epilepticus after treatment, and 8 of complications initiated by the therapy. Data were not available on 7. Necropsy reports on these cases were incomplete. No lesions were demonstrated which could be identified as constant or typical of changes of the muscles or vascular system associated with the passage of electric current.

Various causes of death following EST have been reported. Riese and Fultz[36] reported a case of a 44-year old woman who developed a flaccid paralysis of all 4 extremities following EST. After her fourth treatment she developed hallucinations and died. Non-specific changes in the central nervous system were found. Nielsen[34] reported one death following EST after treating 1100 patients. The patient was a 51-year old woman with an agitated depression. After the fourth treatment her temperature rose to 108° and she went into profound shock, developed convulsions and died in 24 hours without regaining consciousness. Necropsy did not determine the cause of death, but showed areas of subcortical necrosis of the cerebral hemispheres, and early neural degeneration and chromatolysis of the subcortical region of the cerebral hemispheres and basal ganglia. Eyman and Morris[17] reported 3 deaths after EST. Necropsies were performed on all cases. In the first case, cardiac arrest was thought to be the cause of death, a myocardial infarction of the septum and right ventricle, about 2 weeks old, being found. In the second case, death was thought to be due to cardiac failure, since the necropsy revealed extensive arteriosclerotic changes of the coronary vessels and advanced myocardial fibrosis. In the third case the cause of death could not be determined. Careful attention to the cardiac status of the patients to be treated was stressed by the authors.

MEDICAL RISKS INCIDENT TO ELECTRIC SHOCK THERAPY. Kaldeck *et al.*[24], in 1948, reviewed the physical risks of EST on the basis of material on 8082 treatments in 628 patients. Their experience was much the same as that of others already quoted. Their cases included 8 patients with active and 25 with arrested pulmonary tuberculosis. They state that all patients suffering from acute infection should be excluded from EST. This includes upper respiratory infections and local infections. Their one fatal case was an acute glomerulo-nephritis of several days' duration in a 23-year old male who died after his 8th treatment. Physical and laboratory examinations prior to the beginning of treatment had been negative.

MECHANISM OF CARDIAC COMPLICATIONS. Cardiovascular complications are the most important causes of death from EST. Altschule and Tillotson[9], in 1948, discussed the mechanisms underlying cardiac complications. They stated that the increased intrathoracic pressure occurring with a seizure prevents an increase in the difference between the internal and external pressures on the wall of the coronary arteries and may cause a decrease. Brittle coronary arteries are thereby protected from damage. The positive intra-pleural pressure during the seizure retards the passage of blood from the periphery into the heart. The

heart then becomes smaller and its work is decreased. At the end of the convulsion, cardiac work is increased, judging by the acceleration of circulation time. This increase they state is due to the discharge of the accumulated oxygen debt and requires many minutes. The increased work of the heart is spread out in this manner over a longer period and usually does not reach a dangerous level. In the first minute following the convulsion, the blood trapped at the periphery during the seizure rushes into the great veins and the right auricle. This increases cardiac work and may account for the arrhythmias which occur at this time. A decrease in the oxygen debt developed and in the amount of blood concentrated at the periphery could decrease this post-convulsive strain on the heart, the authors postulated. This could be effected by the use of D-tubocurarin. Altschule[3], in 1950, studied further vagal influences on the heart during EST. He concluded that the vagal hyperactivity responsible for the cardiac arrhythmias is activated by several mechanisms. Electric stimulation of the cranium is one. This is usually masked by a tachycardia during the seizure. Hyperventilation provides another which may be reflex in origin. He reviewed two cases of his own without heart disease in which an abnormally sensitive carotid sinus slowed heart rates to 10 to 30 after their first seizure. Atropine abolished the slow rates in subsequent seizures. He emphasized the need to test the carotid sinus mechanisms in all candidates for EST.

Medication Prior to Electric Shock Therapy in Cardiac Diseases. Hayman[19], in 1946, suggested premedication in patients with cardiac disease as a prophylaxis against cardiac complications. He felt that often cardiac complications are preceded by various arrhythmias that may be controlled by quinidine. He also suggested that vasodilator drugs may be useful. Hejtmancik *et al.*[21], in 1949, followed Hayman's recommendation as to quinidine therapy in selected cases for eliminating ectopic rhythms following the convulsion. Prompt administration of oxygen was also effective in their cases. They also commented on atropine as being effective in eliminating alarming cardiovascular and respiratory reactions. They felt that to obtain the desired effect atropine must be given in doses of 1.3 mg. to 2.1 mg. 30 minutes before the stimulus. Because it acts as a respiratory stimulant, post-convulsive apnea was apparently eliminated by such medication. Smaller amounts of atropine, however, were not effective. They also felt that the prophylactic use of atropine was of value in avoiding cardiac arrest, a probable mechanism of some fatal reactions. Retching and vomiting have also been helped. Premedication with atropine was advised only in selected cases, particularly when the pre-treatment electrocardiogram showed prolonged PR intervals, or when post-convulsion arrhythmias and other undesirable vagotonic effects occurred. Bankhead, Torens, and Harris[11], in 1950, discussed the anticipation and prevention of cardiac complications in EST. They felt that atropine is a safe pre-medication and prevents vagal post-convulsive cardiac irregularities. In patients with heart disease the judicious use of digitalis, quinidine, aminophylline, and other supportive medication prior to treatment is of value. Respiratory failure, they felt, is best treated by the early institution of oxygen inhalations with artificial respiration. The authors mention that with the pre-treatment, 4 patients who had suffered acute coronary thrombosis prior to therapy were successfully treated, and 3 others who had suffered episodes of congestive failure and who

were taking digitalis during the course of treatment were also treated uneventfully.

A Study of 192 Patients Treated with Electric Shock Therapy. MATERIAL. A study has been made of 210 series of EST in 192 patients treated on the Neuropsychiatric Service of the Veterans Administration Hospital, Louisville, Kentucky, between April 15, 1946, and January 1, 1952. This represents a total of 3,497 individual electric shock treatments. The patients were divided into age groups, and each age group was studied concerning the findings on medical examination prior to therapy, pretreatment medication, and the medical complications of the EST. In some instances, the patients and their records have been transferred from this hospital and complete data on their cases are not available.

Most of the electric shock treatments in this hospital have been with a Rahm Machine (Serial No. 1071), which gives the standard type sine wave. Stimulations are usually given with 110 volts for .2 second and repeated once or twice within a fraction of a second, inasmuch as previous experience had shown that more than one stimulation were necessary to produce a convulsive reaction. In all cases treatments did produce convulsive reactions.

The course and rate of treatment varied considerably with the type of psychosis, but in general they could be divided into two classes: 1) The schizophrenic group, which included paranoid psychosis, was, in general, treated 3 times a week until a total of 20 treatments had been reached. Occasionally, if the patient became acutely disturbed during a course of treatments, he would be given EST daily for about 4 to 6 days. 2) The other group consisted of the affective disorders and included manic depressive psychosis, involutional melancholia, and reactive depressions. In depressive reactions, treatment again was usually given about 3 times a week until the patient had had 8 to 12 treatments, the actual point of stopping being considered as 2 treatments after the patient had ceased to show signs of improvement. In manic reactions the treatment was in a somewhat different manner, particularly during the early phases of treatment. The manic episodes were treated during the first week usually with one treatment per day and occasionally as many as 3 treatments per day. Treatment was terminated when they had had 12 to 30 convulsive reactions. Again, the point of ending treatment was determined by their clinical response.

All of these patients were seen and examined by a member of the Medical Service prior to EST. A chest roentgenogram, electrocardiogram, blood Kahn, complete blood count, sedimentation rate, and routine chemical and microscopic urinalyses were done. An attempt was made to determine whether or not acute or chronic infection was present. Medical findings of significance were reported to the Neuropsychiatric Service and an opinion was given as to the patient's suitability for EST on the basis of physical and laboratory findings. The final decision lay with the Neuropsychiatric Service, after weighing the psychiatric need against the medical risk.

Results of Study. In the 20 to 30-year age group, there were 78 patients who received 82 series of EST. Findings on preliminary medical examination included hypertension in 2 cases. Various types of arrhythmias and other electrocardiographic abnormalities were encountered. These abnormalities included right and left axis deviation, delayed intraventricular conduction, wandering pacemaker, bigeminal rhythm due to ventricular premature contractions and delayed intra-auricular conduction. Other medical findings included chronic prostatitis, malnutrition, and a history of rheumatic fever. One patient had active pulmonary tuberculosis with cavitation and bilateral pneumothorax.

Premedication was as follows: In 48 series, the patients received atropine alone; in 3, curare alone; in 4, both atropine and curare; and in 27 the pre-treatment is unknown.

Complications in this group of patients were few. The patient with bigeminal rhythm was treated with quinidine, gr. 3, t.i.d., 3 days before and during EST. The bigeminal rhythm persisted during and after treatment. One patient with no previous evidence of renal disease developed cylinduria which cleared up after EST was discontinued. The patient with active pulmonary tuberculosis developed an infiltrate of the left upper lobe, not previously seen on chest film, after 10 treatments. He left this hospital

AWOL less than one month later, and whether or not EST adversely affected his tuberculosis is not known.

In the 30 to 40-year age group, there were 71 series of EST in 62 patients. Findings on medical examination included the following electrocardiographic abnormalities, occurring in one or more cases, each: nodal rhythm, delayed intraventricular conduction, right bundle branch block, left axis deviation and T-wave changes suggestive of myocardial ischemia. Other findings included multiple sclerosis, post-traumatic grand mal epilepsy, pyuria (treated with penicillin during EST), and questionable cortical atrophy.

In 49 series, the patients received atropine alone; in 3, curare alone; in 8, both atropine and curare; and in 11 series the pre-treatment is unknown.

Complications in this group were few. One patient developed atelectasis of the right lung during therapy, was successfully treated medically, and the EST resumed. This patient had no evidence of lung disease prior to or following EST.

In the 40 to 50-year age group, there were 19 series of EST in 17 patients. The medical findings in this group of patients included hay fever in one, clearing atypical pneumonia in one, duodenal ulcer in one, and T-wave changes suggestive of myocardial ischemia in two. One of the patients in this group had had encephalitis due to tetraethyl lead inhalation which was complicated by a toxic psychosis caused by lead poisoning. This patient was admitted in a critical condition on January 1, 1951, immediately following his exposure to tetraethyl lead and was treated with BAL from January 3, 1951, to January 13, 1951, and from January 30, 1951, to February 14, 1951. After a stormy course, he was treated successfully with EST beginning on July 12, 1951.

Of this group, in 12 series, the patients received atropine alone; in none, curare alone; in 2, both atropine and curare; and the premedication was unknown in 5 series.

Complications in this group were again few and not serious. Respirations ceased for 6 minutes in one case and laryngeal stridor occurred twice in one series in a patient who had received curare as pre-medication. In one series the patient developed hemoptysis and substernal pain on the fourth and fifth of a series of 22 EST, the cause of which was not found.

In the 50 to 60-year age group, there were 27 series of EST in 26 patients. The medical findings in this group were numerous. There was hypertension in one patient. Abnormal electrocardiographic findings included delayed intraventricular conduction in one case; low voltage in one; T wave changes suggestive of myocardial ischemia in 3; old posterior infarct in one; right bundle branch block in 2; numerous premature auricular contractions, premature nodal contractions, and occasional ventricular premature contractions in one case. This last patient was treated with aminophylline suppositories 2 to 3 hours before each treatment and he also received Mercuhydrin. There was ankle edema in 2 patients; bronchiectasis in one; controlled diabetes in one; pulmonary emphysema in one; and, in one case the chest film showed fibrous mottling throughout both lung fields. The chest work-up in this case was negative for tuberculosis and the cause of the condition was not determined. In one patient, microscopic hematuria was noted on the initial medical examination, and further investigation revealed a papillary carcinoma of the bladder.

Premedication in these cases consisted of atropine alone in 15 series, curare alone in 4, both atropine and

curare in 6, and was unknown in one series.

Complications in this group were again few. In one case there was slow respiratory recovery on 2 occasions in a patient who had received only atropine. Another case had one delayed respiratory recovery after having received both atropine and curare premedication. In one patient there were hemoptysis and chest pain after 12 treatments, but the chest film was negative and no explanation of these symptoms was found. The diabetic was stabilized on 5 units daily less of insulin after EST. The patient with the abnormal lung findings was transferred to another hospital and no follow-up studies are available.

In the over-60-year age group, there were 11 series of EST in 9 patients. Findings on medical examination were as follows: Ulcerative colitis in remission, one; ulcerative colitis in advanced stage, one; hypertension, two; severe peripheral arteriosclerosis, one; and, T wave changes suggestive of myocardial ischemia in one. In one patient the findings showed low voltage on the electrocardiogram and minimal fibrotic infiltration of the left upper lobe characteristic of tuberculosis. This patient had been studied one year previously, and since there were no positive tests for tuberculosis, he was cleared for EST by the Chest Therapy Board. In another case the patient had cerebral and generalized arteriosclerosis, and had experienced melena one month prior to EST, the cause of which was not demonstrated.

Of this group the patients received atropine alone in 4 series; curare alone in 4; both atropine and curare, in one; and, in 2 series the premedication is unknown.

TABLE 1.—MEDICAL COMPLICATIONS PRIOR TO ELECTRIC SHOCK THERAPY

	Age Groups (years)					
Complication	*20–30*	*30–40*	*40–50*	*50–60*	*60+*	*Total*
EKG abnormalities	8	7	2	9	2	28
Hypertensive vascular disease	2			1	2	5
Pulmonary fibrosis, cause unknown				1	1	2
Pulmonary tuberculosis, active	1					1
Epilepsy, post-traumatic, grand mal		1				1
Pneumonia, atypical, clearing			1			1
Bronchiectasis				1		1
Pulmonary emphysema				1		1
Acute encephalitis due to lead poisoning			1			1
Chronic ulcerative colitis in remission					1	1
Chronic ulcerative colitis, late stage					1	1
Upper G.I. hemorrhage; generalized arteriosclerosis					1	1
Old cerebrovascular accident; generalized arteriosclerosis					1	1
Cortical atrophy		1				1
Carcinoma of bladder				1		1
Pyuria due to unknown cause	1					1
Pyuria (treated with penicillin during EST)		1				1
Diabetes mellitus				1		1
Chronic prostatitis	1					1
Malnutrition; vitamin deficiency	1					1
Hay fever			1			1
Multiple sclerosis		1				1
Duodenal ulcer			1			1
TOTAL	14	11	6	15	9	55

Complications in this age group were also very few. The patient with the late stage of ulcerative colitis developed an aspiration pneumonia but had a good recovery. The chest case was seen 3 times following discharge and had no chest complaints. A chest film was not made however.

Summary of Case Studies. The largest number of treated cases occurred in the 20- to 30 and 30- to 40-year age groups. Schizophrenia, par-

TABLE 2.—ELECTROCARDIOGRAPHIC ABNORMALITIES PRIOR TO ELECTRIC SHOCK THERAPY

	Age Groups (years)					
EKG Changes	*20–30*	*30–40*	*40–50*	*50–60*	*60%*	*Total*
Disturbances of Rhythm						
Numerous auricular prematures, premature nodal contractions, occ. ventricular contraction				1		1
Bigeminal rhythm, ventricular premature contractions	1					1
Nodal rhythm		1				1
Wandering pacemaker	1					1
Disturbances of Conduction						
Delayed intra-auricular conduction	1					1
Delayed intra-ventricular conduction	1	2		1		4
Rt. bundle branch block		1		2		3
Myocardial Abnormality						
Old posterior infarction				1		1
"T" wave changes suggestive of myocardial ischemia		2	2	3	1	8
Left ventricular hypertrophy	1					1
Low voltage				1	1	2
Miscellaneous						
Rt. axis deviation	1					1
Left axis deviation	2	1				3
TOTAL	8	7	2	9	2	28

TABLE 3.—MEDICAL COMPLICATIONS OF ELECTRIC SHOCK THERAPY

	Age Groups (years)					
Complications	*20–30*	*30–40*	*40–50*	*50–60*	*60+*	*Total*
New infiltrate in left upper lobe in pt. with bilateral active TBC	1					1
Aspiration pneumonia					1	1
Atelectasis of the rt. lung		1				1
Hemoptysis and substernal pain (after 4th & 5th of 22 EST)			1			1
Hemoptysis and diffuse chest pain (after 12th of 20 EST)				1		1
Tachycardia (after 1st treatment in pt. with bigeminal rhythm)	1					1
Respirations ceased for 6 min. (after 1st treatment) (No curare)			1			1
Laryngeal strider (2 occasions: curare premedication)			1			1
Cylindruria (which cleared when treatment was stopped)	1					1
TOTAL	3	1	3	1	1	9

ticularly paranoid schizophrenia, predominated in the younger age groups while effective disorders, such as manic depressive psychosis, involutional melancholia and reactive depression, predominated in the older age groups.

Medical examinations and laboratory studies revealed a wide variety of medical disorders. Among these the more important were a case of encephalitis due to lead poisoning, a case of bilateral active tuberculosis, two cases with chronic infiltration of the lungs due to unknown cause, a case of post-traumatic grand mal epilepsy, and one case of advanced chronic ulcerative colitis. Many electrocardiographic abnormalities were encountered.

Few complications occurred, and those which did occur were generally not serious. Whether or not the EST adversely affected the patient with active tuberculosis is not known. Atropine as premedication was used in the majority of patients. This may account, at least in part, for the absence of cardiac complications. There were no deaths in this study which could be attributed either directly or indirectly to EST.

Although this paper is concerned primarily with the medical aspects of EST, some mention of orthopedic complications should be made. The most frequent complication seen is compression fracture of the spine. In older patients with general debility such a fracture can be a serious matter, especially when added to other chronic illness. In our study all patients had roentgenograms of the spine and were seen by a member of the Orthopedic Service who gave an opinion as to the risk involved in each patient and advised concerning premedication for the prevention of this complication when indicated. There were 7 compression fractures of the spine in our patients, representing an incidence of 3.6%. Two were in the 20 to 30-year age group, 3 in the 30 to 40-year group, one each in the 40 to 50-year and 50 to 60-year groups, and none in the over-60-year group. In addition there was one fracture of the surgical neck of the humerus in the 30 to 40-year group.

Discussion. From a review of the literature and the study of our own cases, it is evident that EST is a reasonably safe method of treatment of psychiatric patients, even in patients with chronic medical illness, provided reasonable precautions are taken. True medical contraindications are few. A good physical examination and laboratory studies as previously described must be done to evaluate adequately the patient's physical status. The most important considerations are heart disease, acute and chronic infectious processes, peripheral vascular disease, and recent coronary or cerebrovascular accidents. If at all possible, infectious processes should be treated by the best means available before EST and the patient should be observed for recurrence during and after therapy. Often a psychotic patient is uncooperative and effective treatment of his medical disorder may be impossible. In such cases the patient, in his psychotic state, may aggravate whatever disease exists and may even endanger his own life. Accordingly, the need for EST must be weighed carefully against the risk involved.

Patients with heart disease should be prepared for EST by appropriate methods. Congestive failure should be compensated by the use of digitalis, salt restriction, and mercurial diuretics. Abnormalities of rhythm which are responsive to quinidine or Pronestyl should be treated prior to, and during EST. Atropine is a useful drug as premedication, because it tends to prevent or lessen the incidence of arrhythmia following treatment and cuts down the risks in patients known to have heart

disease. Our patients showed many of the electrocardiographic abnormalities commonly encountered, and our findings support the concept that these patients can be successfully treated. Curare (D-tubocurare) may be useful in protecting the heart during the crucial minutes following the convulsive seizure.

Summary and Conclusions. 1) A review of the literature on electric shock therapy (EST) reveals the following considerations of medical import:

a) Cardiovascular effects of EST include many types of rhythm disturbances and ectopic beats, due probably to increased vagus tone, which can be abolished by the use of atropine. The systolic blood pressure rises at first, but after 6 to 7 treatments, there is a systolic and diastolic hypotension, due to loss of vasomotor tonus, with gradual return to pre-treatment levels.

b) The effects on extracellular fluid balance, water metabolism, and eosinophile count resemble those which occur after the administration of the 11-oxysteroids, but remissions are not the result of increased secretion of these hormones.

c) Central nervous system changes are probably temporary and physiologic rather than permanent.

d) Patients with cardiovascular disease, active tuberculosis, thyrotoxicosis, central nervous system disease, and hypertension can be successfully treated with EST.

e) Contraindications to EST include heart failure, recent myocardial infarction and aneurysm of the aorta. There is also a significant risk of worsening the patient's physical condition in the presence of recent cardiovascular accident, acute respiratory infection, and active peripheral vascular disease.

f) Cardiac complications are the most important cause of death following EST. Trapping of blood at the periphery and accumulated oxygen debt, followed by the rush of the trapped blood into the great veins and right auricle may account for some of the complications. In patients with heart disease, digitalis, quinidine, and aminophylline are useful as premedication. Atropine given in adequate doses 30 minutes before treatment may prevent alarming cardio-respiratory reactions.

2) A review of 210 series of EST in 192 patients treated at the Veterans Administration Hospital, Louisville, Kentucky, is here reported.

a) Co-existing diseases in this group of patients included encephalitis due to lead poisoning; bilateral active pulmonary tuberculosis; chronic infiltration of the lung of unknown cause; post-traumatic epilepsy; advanced ulcerative colitis; and electrocardiographic abnormalities.

b) Treatment produced few complications, usually not serious and none fatal.

c) Atropine was used as premedication in the majority of patients.

d) Complications are best avoided by careful study of patients before treatment.

e) In the presence of organic disease, the psychiatric need must be weighed against the risk involved in each case.

3) Electric shock therapy is a safe method of treating psychiatric patients, provided reasonable precautions are taken in the selection and preparations of cases, and provided appropriate pre-treatment medication is used.

REFERENCES

1. **Alexander, L.**, and **Lowenback, H.**: J. Neuropath. & Exper. Neurol., 3, 139, 1944.
2. **Alpers, B. J.**, and **Hughes, J.**: Arch. Neurol. & Psychiatry, 47, 383, 1942.

3. **Altschule, M. D.:** Am. Heart J., **39**, 88, 1950.
4. **Altschule, M. D., Altschule, L. H., and Tillotson, K. J.:** J. Clin. Endocrinol., **9**, 548, 1949.
5. **Altschule, M. D., Ascoli, I., and Tillotson, K. J.:** Arch. Neurol. & Psychiatry, **62**, 618, 1949.
6. **Altschule, M. D., and Cline, J. E.:** Proc. Soc. for Exper. Biol. & Med., **69**, 598, 1948.
7. **Altschule, M. D., Gans, J. E., and Tillotson, K. J.:** Arch. Neurol. & Psychiatry, **59**, 476, 1948.
8. **Altschule, M. D., Parkhurst, B. H., and Tillotson, K. J.:** J. Clin. Endocrinol., **9**, 440, 1949.
9. **Altschule, M. D., and Tillotson, K. J.:** New England J. Med., **238**, 113, 1948.
10. Iidem: Am. J. Psychiatry, **105**, 829, 1949.
11. **Bankhead, A. J., Torrens, J. K., and Harris, T. H.:** Ibid., **106**, 911, 1950.
12. **Barker, P. S., Shrader, E. L., and Ronzoni, E.:** Am. Heart J., **17**, 169, 1939.
13. **Berrera, S. E., Lewis, N. D. C., Pacella, B. L., and Kalinowsky, L.:** Tr. Am. Neurol. Assn., **68**, 31, 1942.
14. **Bellet, S., Kerchbaum, A., and Furst, W.:** Am. J. Med. Sci., **201**, 167, 1941.
15. **Clute, K. F., and Fitzgerald, B. A.:** Canad. Med. Assn. J., **59**, 426, 1948.
16. **Doan, D. I., and Huston, P. E.:** Psychiatric Quart., **22**, 413, 1948.
17. **Eyman, E. V., and Morris, H. H., Jr.:** Arch. Neurol. & Psychiatry, **64**, 263, 1950.
18. **Goodman, L.:** J. Nerv. & Ment. Dis., **112**, 139, 1950.
19. **Hayman, M.:** Am. J. Psychiatry, **102**, 316, 1945.
20. **Heilbrunn, G., and Weil, A.:** Arch. Neurol. & Psychiatry, **47**, 988, 1942.
21. **Hejtmancik, M. R., Bankhead, A. J., and Herrmann, G. R.:** Am. Heart J., **37**, 790, 1949.
22. **Igersheimer, W. W., and Stevenson, J. A.:** Arch. Neurol. & Psychiatry, **65**, 740, 1951.
23. **Kaldeck, R.:** Ibid., **59**, 229, 1948.
24. **Kaldeck, R., McLaughlin, W. F., Gurri, J., and Wassersug, J. I.:** New England J. Med., **239**, 773, 1948.
25. **Kalinowsky, L. B., and Hock, P. H.** (who cite Cerletti and Beni): Shock Treatment. New York, Grune & Stratton, Inc., p. 5, 1946.
26. **Karliner, W.:** J. Nerv. & Ment. Dis., **107**, 1, 1948.
27. **Keefer, C. E.:** Arch. Int. Med., **45**, 1, 1930.
28. **Kleinschmidt, J., Miller, J. S. A., Orens, M. H., and Cohen, L.:** Psychiatric Quart., **23**, 145, 1949.
29. **Kline, E. M., and Fetterman, J. L.:** Am. Heart J., **24**, 665, 1942.
30. **Loftus, T. A., Gold, H., and Diethelm, O.:** Am. J. Psychiatry, **101**, 697, 1944.
31. **Mainzer, F., and Krause, M.:** Brit. Heart J., **2**, 221, 1940.
32. **Moore, M. T.:** Arch. Neurol. & Psychiatry, **57**, 697, 1947.
33. **Newberger, K. I., Whitehead, R. W., Rutledge, E. K., and Ebaugh, F. G.:** Am. J. Med. Sci., **204**, 381, 1942.
34. **Nielsen, J. M.:** Bull. Los Angeles Neurol. Soc., **15**, 200, 1950.
35. **Plice, S. G., and Pfister, C. W.:** Am. Heart J., **40**, 252, 1950.
36. **Riese, W., and Fultz, G. S.:** Am. J. Psychiatry, **106**, 206, 1949.
37. **Stern, K., Askonas, B. A., and Culling, A. M.:** Ibid., **105**, 585, 1949.
38. **Straker, M.:** J. Mental Sci., **90**, 780, 1944.
39. **Thorn, G. W., Forsham, P. H., Pruntz, F. T. G., and Hill, A. G.:** J. Clin. Endocrinol., **8**, 15, 1948.
40. Iidem: J. Am. Med. Assn., **137**, 1005, 1948.
41. **White, P. D., Chamberlain, F. L., and Graybiel, A.:** Brit. Heart J., **3**, 233, 1941.
42. **Will, O. A., Jr., Rehfeldt, F. C., and Newman, M. A.:** J. Nerv. & Ment. Dis., **107**, 105, 1948.
43. **Williams, R. L., and Barrera, S. E.:** Psychiatric Quart., **24**, 800, 1950.
44. **Winkelman, N. W., and Moore, M. T.:** J. Neuropath. & Exper. Neurol., **3**, 199, 1944.

PSITTACOSIS*

By W. W. G. Maclachlan, M.D.
PROFESSOR OF MEDICINE

G. E. Crum, M.D.
ASSISTANT PROFESSOR OF MEDICINE

R. F. Kleinschmidt, M.D.
INSTRUCTOR OF MEDICINE

AND

P. F. Wehrle, M.D.
RESEARCH ASSOCIATE IN EPIDEMOLOGY

(From the Medical Department of the Mercy Hospital and the University of Pittsburgh School of Medicine and Graduate School of Public Health, Pittsburgh, Pennsylvania.)

We have had the opportunity during the past year of seeing 10 individuals who presented clinical or serological evidence of having had psittacosis. There was contact with a parakeet in 7 of the cases. One of them died of pneumonia on the 6th or 7th day of the illness. A marked variation in the clinical picture of the disease was noted in this small group of cases.

Case Reports. CASE 1. On November 14, J. N., a 58-year old male who was a mechanic in a railroad shop, was admitted to the Mercy Hospital in a very toxic condition due to pneumonia of both lungs. He had a pleural and a pericardial rub on the left with typical signs of consolidation of the upper and lower lobes of the left lung and the lower lobe of the right lung. He showed pulmonary edema, a pulse rate of 140 plus, cyanosis of some degree and slight stiffness of his neck. He died in about 20 hours after admission, having received in this short time massive doses of penicillin in the muscle; 6 million units, and 2 gm. of aureomycin in the vein. His leukocyte count was 10,800. The blood culture was negative and no pathogenic bacteria were grown from the sputum. Blood urea nitrogen was 23 mg. per 100 cc. of blood and the spinal fluid was normal. He died on November 15, shortly after admission, on either the 6th or 7th day of his illness, according to the history given by his wife. The man had refused to go to bed until he was brought home from his work on the night of November 13, and on the following day saw his physician, Dr. M. Shapiro, who made the diagnosis of pneumonia and sent him at once to the hospital, after giving him an injection of 300,000 units of penicillin. At the time of his death from his clinical signs we considered pneumococcic lobar pneumonia to be the most likely cause of his illness. The Roentgen-ray showed a massive shadow on the left and the lower lobe of the lung on the right. When his wife gave permission for a necropsy, she told us that two of her children were also ill at home, and then we inquired about the presence in the home of a parrot or parakeet. Three weeks before the man's death his son had bought a parakeet at a 5 and 10 cent store in Weirton, West Virginia and had taken it to their home in East Pittsburgh. The bird was apparently well. At necropsy, pneumonia was noted in both lobes of the left lung and in the lower lobe of the right lung. A good part of the consolidation was in the red hepatization stage. There was a well marked fibrinous pleuritis on the left and also a fibrinous pericarditis. The other important positive finding was a large, 500 gm., rather soft, reddish spleen. Microscopically, the pneumonia was chiefly a mononuclear one with some polymorphonuclear cells present. There was marked congestion of the capillaries in the alveolar walls, but there was no evidence of any prominence of the epithelial lining alveolar cells as we had seen in a previously reported case of psittacosis. There was no atelectasis present, nor

* Read before the Association of American Physicians, May 5, 1953, at Atlantic City.

was there any thrombosis of the small vessels of the lung. Cultures taken at necropsy from the lung were sterile.

The parakeet was killed the day after the necropsy by anesthesia and it was sent by Dr. Wehrle to the United States Public Health Virus Laboratory in Montgomery, Alabama, along with a piece of the lung and of the spleen from the necropsy. From all 3 sources the psittacosis virus was grown.

CASE 2. Gloria N., aged 17, had been perfectly well on Wednesday, November 12, 1952, but on Thursday morning she had awakened with an intense headache which was her only symptom and it remained for about 5 days. She had no cough nor sputum. There was fever over a 4-day period, reaching to 103° at its highest. She had, at first, rales in the right lower lung and on the 5th day of the disease there was blowing breathing in the upper part of the right lower lobe of the lung, but all physical signs disappeared in 3 or 4 days. She was given at home 300,000 units of penicillin in the muscle, once on the 2nd day and twice on the 3rd and 4th day of her illness, and for the next 5 days in the hospital, 2 gm. of aureomycin daily by mouth. She had no fever at the end of the 4th day. During her hospital stay of 6 days she was not in the least ill save for some headache for the first 2 days. On the 10th day of her illness we noted a palpable spleen which was very definite. We had carefully watched for this physical sign and during this time she was taking a large dose of aureomycin 2 gm. per day. We may, therefore, perhaps infer that the spleen enlarged even while under this therapy. The leukocytic count was 5,500 with polymorphonuclears 70%, lymphocytes 28%, monocytes 1% and eosinophils 1% on the 5th day and 7,900 with polymorphonuclears 77%, lymphocytes 20% and eosinophils 3% on the 9th day of the illness. There was a trace of albumin in the urine. The roentgenogram of the chest showed a very definite shadow on the right which had almost cleared by the 9th day. Her blood serum showed a positive complement fixation for the psittacosis-lymphogranuloma venereum group at the Pennsylvania State Virus Laboratory in Philadelphia on the 17th day from the onset of her illness. The spleen could not be felt on the 18th day of the disease when she returned to the hospital for an examination.

CASE 3. Guy N., a boy of 14 years, took sick on November 11 with a very sore throat which remained for 5 days. He had no other symptom. He had a slight fever of 102° for 2 days but there was no headache, cough nor chilly sensation. He was given at home, a daily injection of 300,000 units of penicillin for 2 days on the 4th and 5th days of his illness, and as he then appeared to be well the penicillin was stopped. We did not see him at the hospital until the 7th day after the onset. He was afebrile and had no symptoms. The tonsils were of normal color but rather large. There were no palpable lymph nodes in the neck or axilla, but rather large, very easily palpable spleen was present. The chest was clear and the roentgenogram of the chest was normal, but this was taken on the 7th day of his illness. Ten days later or the 17th day of his illness one could just feel the edge of the spleen. This boy had 7,950 leukocytes in his blood count with 71% polymorphonuclears, 28% lymphocytes and 1% eosinophils on the 6th day of his illness. His complement fixation also was positive for the psittacosis-lymphogranuloma venereum group at the Pennsylvania State Virus Laboratory in Philadelphia. He was never admitted to the hospital and received only 2 injections of penicillin at his home.

CASES 4 and 5. The Mother, Mrs. N., was always perfectly well but her blood serum which Dr. Wehrle took showed a positive complement fixation for the psittacosis-lymphogranuloma venereum group.

The daughter-in-law who lived at their home also was quite well but her blood serum similarly showed a positive psittacosis-lymphogranuloma venereum complement fixation. The only member of the family who was not ill and who refused to have the blood taken for testing was the young man of 24 who had bought the parakeet as a present for his wife. We did not have the opportunity to examine these 3 members of the family.

CASE 6. A woman of 45 years, on the medical service of Dr. Crum, was admitted to the hospital on the 6th day of her illness, November 29, 1952 with fever, aching muscles and severe headache. The signs in the chest were very few, only an occasional rale in the left lower axilla, but the Roentgenray showed a definite shadow in the left lower lobe of lung. They had bought a parakeet about the middle of October. The bird had always appeared well. The patient was free from fever after the 4th day in the hospital which was the 10th day of the illness. The spleen was never palpated. She went home quite well and free of symptoms or signs. The leukocyte count showed 10,600, 11,400 and 4,900 with normal differentials on two of the counts. There was a trace of albumin in the urine and the blood urea nitrogen was 16 mg. per 100 cc. The blood serum showed a positive reaction in the

complement fixation for the psittacosis-lymphogranuloma venereum group but the parakeet which had been killed and sent by Dr. Wehrle to the United States Public Health Virus Laboratory in Montgomery, Alabama, failed to show any virus on culture.

CASE 7. The patient was a man of 36 years, who had driven in his automobile from Florida with his wife and sister-in-law and in addition 6 parakeets in cages. They left February 1st and 13 days later the man was ill with headache, chills, fever and muscular aching. He had a slight cough, but no sputum. He was very sick at home for one week with a high fever due to a pneumonia of the left lower lobe of the lung. He was admitted to the hospital on the 8th day of his illness with temperature 104.2° pulse 100, respiration 28, and 7,300 leukocytes with 85% polymorphonuclears, 14% lymphocytes and 1% eosinophils. He had a crisis on the 9th day. The spleen was never palpable. He had received penicillin and aureomycin at home and the latter was continued at the hospital. He made a good recovery and left the hospital on the 14th day of his illness. Three of the parakeets had been given to friends, one had died the day after arriving home and was not examined further but the 2 other birds were sent for examination by his family physician to the Pennsylvania State Virus Laboratory and from there to the United States Public Health Virus Laboratory at Montgomery, Alabama. The psittacosis virus was isolated from both parakeets. This man appeared to make a perfect recovery. The roentgenogram on the 8th day of the illness showed a shadow in the middle third of the left lung field of pneumonia and by 4 days later the shadow had almost disappeared. The complement fixation test was positive for the psittacosis-lymphogranuloma venereum group at the Pennsylvania State Virus Laboratory on the 16th and 28th day after the onset of his symptoms.

The 8th, 9th and 10th cases were of interest, in that, they could be grouped as atypical pneumonia patients. They were seen during March, July and December 1952.

CASE 8. A man of 54 years was admitted on his 7th day of illness with a temperature of 104.3°, pulse 100 and respiration 24. He had a crisis on the 8th day. He was treated with penicillin, and was febrile, in the hospital, for only one day. His leukocyte counts were 7,700 and 6,200 with a normal differential. His illness began with headache, fever and chilly sensations. He had had no antibiotics at home. The chest showed no definite physical signs but there was a slight change in the right lung shadow at the hilar area in the Roentgen-ray. The blood culture was negative and pneumococcus was noted in the sputum but it was not of Type 1 to 34. The spleen was easily palpable for a period of 4 days from the time of his admission. On account of this splenic enlargement we sent the serum to the Pennsylvania State Virus Laboratory on the 10th and 27th days of his illness and there was a positive complement fixation in increasing titer for the psittacosis-lymphogranuloma venereum group. The man denied any contact with birds.

CASE 9. A man, 38 years old, was admitted to the hospital on the 2nd day of his illness. He had a slow lysis course of fever over 11 days. The fever never was higher than 102°, pulse rate 80 and respirations 20. Leukocytes numbered 10,500. Sputum and blood culture were negative. There were physical signs of rales in the left lower lobe and this involvement of the lung was confirmed by Roentgen-ray. The spleen was not palpable. He did not respond to pencillin. He had a positive complement fixation at the Pennsylvania State Virus Laboratory for the psittacosis-lymphogranuloma venereum group. There was no history of contact with birds in this case. Clinically, he represented an atypical pneumonia, having a slow fall to normal temperature over 11 days, never very ill and showing no special response to penicillin.

CASE 10. A man of 54 years who had an acute respiratory infection between Christmas and New Year's Day. He was at home and was given penicillin, sulfadiazine and later aureomycin. After a week of aureomycin he became very nauseated and had abdominal pains and diarrhea. His respiratory infection became somewhat chronic so far as coughing and sputum were concerned so he came into the hospital where he remained for 3 weeks. He had plenty of rales at the lower lobe of the left lung and a definite shadow in this area by the Roentgen-ray. The leukocyte count was 5,400 with polymorphonuclears 61%, lymphocytes 34%, eosinophils 4% and monocytes 1%. He was given penicillin for one week in a large dosage. He made a good recovery and his chest was cleared of rales and the Roentgen-ray was normal. He never had a palpable spleen. The urine was normal. Two specimens of blood serum have shown a marked positive complement fixation for the psittacosis-lymphogranuloma venereum group. There is no history of any contact with birds in this case.

Discussion. One is impressed by the great variation in the clinical appearance and in the toxicity of the disease in different people. Seemingly, young adults take psittacosis in a much milder form than older people. It is true that our fatal case never stopped work or even went to bed until 24 hours before his death, but this was due to his own stubbornness as he had never been ill prior to this time and was unaware of the seriousness of what he was doing. In any form of pneumonia this neglect might prove to be very serious or even fatal. In fact in our experience with pneumococcic pneumonia, which is still frequent in our clinic, the majority of the fatal cases are the medically neglected ones that keep walking about until they either die on the street or live only a few hours after admission to the hospital. Perhaps if this patient had been willing to go to bed several days sooner, as his wife wished him to do, the outcome might have been different. Intense headache appears to be a rather common symptom at the onset of psittacosis, but this is noted in other virus infections such as influenza. It is interesting that the boy of 14 only presented a severe sore throat while his sister of 17 had practically nothing other than a headache. The other 3 members of the family were never sick, but 2 of them showed positive complement fixation tests for the psittacosis-lymphogranuloma venereum group, as the 24-year-old son refused to have the blood taken for testing. A single case of psittacosis in a family should, therefore, raise one question of the presence of other cases if the source, the parakeet, is in the same house. It may be very difficult to establish the history of bird contact and as Meyer[11] has shown ducks, chickens and pigeons may all be involved in this disease. Smadel[14], in 1943, reported 10 positive complement fixation cases for the psittacosis-lymphogranuloma venereum group in 45 atypical pneumonias, and 4 of this number were in contact with pigeons. We believe this observation is significant and in every atypical lung infection we should inquire about the bird contact history because we are of the opinion that at the present time neither by the physical examination nor by roentgenogram of the lung are we able to diagnose psittacosis.

We have been impressed, however, with the significance of an enlarged spleen as a most helpful sign, both pathologically and clinically, of the virus infection of psittacosis. In our present fatal case the spleen weighed 500 gm. which is over three times the normal. A few days after the necropsy on the psittacosis case we had a pneumococcic pneumonia patient die just after he was admitted to the ward, and it was not in the least unusual in this type of case that he had walked some distance to the hospital. This patient had a positive blood culture, showing 600 colonies of pneumococci (Type II) per 1 cc. of blood on the blood agar plate. He had had no medical treatment outside. His spleen at necropsy was small as it weighed only 120 grams. It is well known pathologically that uncomplicated pneumococcic pneumonia rarely causes the spleen to be enlarged to any great degree. Osler[12] mentioned in the first edition of his text book on the postmortem findings of pneumonia, "The spleen is often enlarged, though in only 35 of the 100 cases was the weight above 200 grammes." Krumbhaar[8] considered 155 gm. as being the average normal weight for the adult spleen. McCrae, Fyshe and Ainley[10] in an analysis of 486 cases of pneumonia and 100 necropsies stated that in uncomplicated pneumococcus pneumonia it was unusual to find splenic enlargement but with mixed infections of the lung a larger

than normal spleen was more frequently found at necropsy.

As a clinical physical finding a palpable spleen has been very unusual in pneumonia in our experience. Three of our cases of psittacosis have shown palpable spleens but they do not appear until toward the end of the first week and they may be palpable only for a few days. It is our present view that the palpable spleen in a case of acute respiratory infection is of considerable diagnostic significance and may be the only sign which would lead one to suspect psittacosis. In the 1918 influenza epidemic in studies from the University of Pittsburgh, Klotz[7] reported on the necropsy findings that in only 2 of 32 cases was the spleen slightly enlarged. We have noted in the past an occasional case of atypical pneumonia with a palpable spleen and considered it to be, on a clinical basis, a post-influenzal infection, which was probably wrong as it more likely was an example of psittacosis. Rivers and Berry[13] showed that in experimentally produced psittacosis the spleen was enlarged and involved in the disease. In the young girl of 17, we found a palpable spleen on the 10th day. We had been carefully watching for it from the 4th day. Furthermore, this patient was taking 2 gm. of aureomycin daily so it might suggest that the splenic enlargement went on irrespective of the aureomycin. In the boy of 14 with the single symptom of sore throat for 5 days we have stated that his blood showed no lymphocytic increase nor did he have any lymph node enlargement except the faucial tonsils and the palpable spleen. He was not a case of mononucleosis. In our previous report on 3 cases of psittacosis the spleen was enlarged to twice the normal size in the fatal case as noted at necropsy and easily palpable in the girl of 9 who had a rather mild illness. In a few cases where we have had serological evidence of the influenza virus infection as reported by the Pennsylvania State Virus Laboratory, the cases clinically have never shown palpable spleens. It is a very easy error to miss feeling a slightly enlarged spleen or worse to neglect to examine the patient for this physical sign. In acutely ill pneumonic patients with distended or rigid abdomens it is futile to attempt to feel the spleen. Further, if one cannot palpate the spleen with the patient lying flat on his back it is essential to have him turn on his right side. We would repeat that this should be done daily particularly in the atypical types of pneumonia. Perhaps this may be the most distinctive physical sign to suggest the possibility of psittacosis and so have serological virus tests done. The enlargement of the spleen, as indicated by its being palpable, is present only for a relatively few days, and could, therefore, be easily missed.

The histological picture of the lung in the case of psittacosis which we[9] reported in 1930 showed in addition to a mononuclear pneumonia a peculiar hyperplasia of the epithelial lining of the alveoli, in fact, nuclear figures were seen in some of the cells. This we considered at the time to be the most distinctive microscopic finding in the pneumonia of our case of psittacosis. There was also considerable atelectasis and some thrombosis of the small blood vessels in the alveolar walls. These findings were noted by other observers at that time especially Hutchinson, Rowlands and Simpson[6] while more recently Binford and Hauser[2] observed the same reaction. The necropsy was done on the 10th day of the illness and this perhaps accounts for the difference in the microscopic picture in our present case who was either 6 or 7 days ill with his pneumonia and showed little other than a mononuclear exudate with some polymorph-

onuclear cells. There was no atelectasis nor thrombosis of small vessels and not the slightest change in the alveolar epithelium. A good part of the lung was still in the red hepatization stage. In experimentally produced psittacosis, Rivers and Berry[13] noted the prominence of the alveolar epithelium.

Our fatal case had been given 1 injection of 300,000 units of penicillin 4 hours before he was admitted to the hospital. He lived about 20 hours after admission and appeared clinically to be hopelessly ill during this period. His blood culture, taken before any more antibiotic was given, was negative. In our pneumonic cases a negative blood culture, as late as this patient was in his illness and in the absence of any antibiotics, almost rules out the pneumococcus as the etiological factor. The beta hemolytic streptococcus in blood culture in the adult pneumonia case in our experience has been very infrequent. After antibiotics have been given a negative culture may mean little. The roentgenogram and the leukocyte count are in no way distinctive as to etiology in such a case as this fatal one. No accurate information regarding a palpable spleen was possible due to the abdominal distention. One may have a suspicion of a severe virus infection from the negative blood culture, but this observation cannot be made for at least 24 hours, and fulminating or terminal cases may be dead by that time. The history of a parrot contact in a case similar to our fatal one is of the greatest significance, although a large spleen associated with a pneumonia at the necropsy table is in itself very suggestive of psittacosis without the history, but it makes the diagnosis almost certain with a positive parrot contact. In the other clinical cases of our group the chest film and leukocyte counts were not diagnostically distinctive, as similar shadows of some consolidation and low leukocyte counts are noted in many of our present types of lung infection. In the past few years the leukocyte counts in pneumonia have lost most of their diagnostic and prognostic significance in that so many, even in proved pneumococcic cases are within normal numbers, and with antibiotics the patient recovers as readily as if a good leukocytosis had been present. It is in this type of mild lung infection, an atypical pneumonia, that a palpable spleen may be of so much value and may lead to the study of the blood serum for antibodies of a virus infection such as psittacosis.

The apparent present increase in atypical pneumonia and the almost ubiquitous administration of antibiotics to any acute respiratory infection render routine bacteriological studies of sputum and blood uncertain, if not at times ineffective. Thus, accurate interpretation of our pneumonia is becoming very difficult, as so many conditions may imitate the atypical pneumonias. Hence the help from the virus laboratory is of great value, even if the reports are only received some time after the acute cases have left the hospital. Clinically, we should attempt to screen our cases as much as possible because it could be a very easy matter to flood a virus laboratory with needless requests. Furthermore, there is a great need for early and rather intensive bacteriologic study of the sputum in our present day pneumonias. As the antibodies may develop slowly, the specimens of blood should be taken on discharge from the hospital which now is usually in 7 to 10 days, and for the 2 later specimens at 2 or 3 weeks' interval after discharge. To be able in the future to take advantage of the opportunity of having virus serological studies made on our doubtful group of atypical pneumonias cannot be other than a very helpful and in-

teresting addition to the better understanding and treatment of acute respiratory infections.

Psittacosis is a very definite public health problem and it is a real danger. At the time of our previous cases, 1930, human to human transmission of the disease was hardly known, but it was referred to by 3 observers, Hutchison *et al.*[6], Horder and Gow[5], and Hegler[4]. However, in more recent years, Eaton Beck, and Pearson[3] reported a remarkable occurrence of human to human infection. From one fatal case which had been diagnosed as influenzal pneumonia 3 nurses took the disease and 2 of them died. Further, 2 laboratory workers on the pathological and bacteriological problems of these cases also developed psittacosis but recovered. We would emphasize, therefore, that human contact with an active case carries some danger, probably through coughing and sputum. Rivers and Berry[13] have shown that the psittacosis virus can be isolated from the sputum. In none of our cases was there any evidence of this type of contact and no laboratory workers were involved. It might be worth while for all laboratory workers, pathological and bacteriological, and the nursing and medical personnel of a pneumonia ward to have complement fixation tests done on themselves. McCoy[1] commented on the frequency of infections with the psittacosis virus noted among his own laboratory group in 1930. It was thought to be air-borne through the respiratory system. Meyer[11], who has contributed so much to our knowledge of psittacosis, has referred to the considerable number of human to human cases reported and to the fact that many of them have been fatal. We are aware of one fatal human transmission case in a nurse a few years ago and there are probably more that were never recognized or if so never reported.

Conclusions. 1. Psittacosis is a preventable disease and in older adults it may be a serious pneumonic infection. From a very small clinical experience we are unable to say what effect the antibiotics had on the infection, but we would recommend that they be given. Our best results were with penicillin.

2. Psittacosis is associated with enlargement of the spleen. This is noted experimentally in animals and birds, pathologically at necropsy in the human and clinically especially in atypical pneumonias in the latter part of their illness for a few days' duration. This last finding may be of considerable diagnostic value and lead to virus complement fixation tests to confirm the diagnosis of psittacosis.

ACKNOWLEDGMENT: We wish to thank Dr. M. Michael Sigel, formerly of the Pennsylvania State Virus Laboratory at the Children's Hospital, Philadelphia, Pennsylvania; now of the U. S. Public Health Service, Montgomery, Alabama, for his interest and aid in our work.

REFERENCES

1. **Armstrong, C., McCoy, G. W., and Branham, S. D.:** U. S. Public Health Rep., **45**, 725, 1930.
2. **Binford, C. H., and Hauser, G. H.:** Ibid., **59**, 2, 1363, 1944.
3. **Eaton, M. D., Beck, M. D., and Pearson H. E.:** J. Exper. Med., **73**, 641, 1941.
4. **Hegler, C.:** Deutsche med. Wchnschr., **56**, 148, 1930.
5. **Horder, T., and Gow, A. E.:** Lancet, **1**, 443, 1930.
6. **Hutchison, R., Rowlands, R. A., and Simpson, S.:** Brit. Med. J., **1**, 633, 1930.
7. **Klotz, O.:** Publications from the University of Pittsburgh School of Medicine, 207, 1919.
8. **Krumbhaar, E. B., and Lippincott, S. W.:** Am. J. Med. Sci., **197**, 344, 1939.
9. **Maclachlan, W. W. G., Permar, H. H., and Rogers, C. A.:** Ann. Int. Med., **4**, 260, 1930.
10. **McCrae, J., Fyshe, J. C., and Ainley, W. E.:** Montreal Med. J., **33**, 19, 1904.
11. **Meyer, K. F.:** Clinical Tropical Medicine. St. Louis, C. V. Mosby, 341, 1951.
12. **Osler, W.:** Practice of Medicine. New York, D. Appleton & Co., 516, 1892.
13. **Rivers, T. M., Berry, G. P., and Sprunt, D. H.:** J. Exper. Med., **54**, 91, 144, 1931.
14. **Smadel, J. E.: J. Clin. Invest., 22, 57, 1943.**

A COMPARATIVE STUDY OF THE EFFECTS OF THREE VASODILATOR DRUGS, PENTAMETHONIUM BROMIDE (C-5), DILATOL (SKF-1700-A) AND PENDIOMIDE (BA-9295) ON THE DIGITAL CUTANEOUS BLOOD FLOW.*

By Herbert L. Needleman, M.D.

and

Orville Horwitz, M.D.

(From the Vascular Section of the Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.)

The usefulness of a drug for digital cutaneous vasodilatation depends on the selectivity of its site of action. Agents causing widespread dilatation in areas other than the skin of the extremities will tend to: (1) divert blood away from the skin of the digits; (2) cause cutaneous reflex vasoconstriction by causing a decrease in blood pressure; or (3) cause an increase in cardiac output which is disadvantageous in cardiac disease so often coexistent with peripheral vascular disease. This concept was discussed by Montgomery in 1942[8], and has recently been termed hemometakinesia[4].

This study was attempted in order to evaluate the specificity of three agents, pentamethonium bromide (C-5), Dilatol (SKF-1700-A), and Pendiomide (BA-9295) for digital cutaneous vasodilatation under controlled environmental conditions. Pentamethonium bromide, or C-5, and its higher analogue, hexamethonium bromide, or C-6, are known ganglionic blocking agents. They are reported to be of value in the treatment of peripheral vascular disease[1]. SKF-1700-A is a suprifen derivative of epinephrine, and has been reported to increase the blood flow to the skin and muscle of experimental animals[9]. BA-9295, a quaternary ammonium compound, has been employed in the treatment of carotid sinus syncope by autonomic blockade[6], and in the treatment of hypertension[3]. Baikie and Smith[2] also found that intravenous BA-9295 produced an increase of temperature of the fingers and toes in an uncontrolled ambient temperature.

The criterion for an increase in the digital cutaneous circulation was an increase in the digital skin temperature in the presence of a controlled environmental temperature. In this study we have attempted to differentiate between cutaneous vasodilatation and vasodilatation elsewhere. The criteria we used to indicate an increase in the circulation other than in the skin were increased pulse rate, decreased blood pressure, and increased cardiac output.

Subjects, materials and methods. Subjects were chosen from patients of the Vascular Section and wards of the Hospital. Some had peripheral arterial disease of varied nature

* This work was made possible by Research Grants from Smith, Kline & French, Inc. and the Ciba Company.

We also wish to thank the following pharmaceutical houses for generous supplies of drugs: Burroughs, Wellcome & Co. for C-5, Smith, Kline & French, Inc. for SKF-1700-A and the Ciba Co. for BA-9295.

TABLE 1.—CHANGES INDUCED BY THREE VASODILATOR DRUGS, C-5, SKF-1700-A AND BA-9295

								Changes Induced					
Subject	*Date*	*Age-Sex*	*Wt. (Kg.)*	*Ht. (inches)*	*Diagnosis*	*Room Temp. ° C.*	*Dose (mg.)*	*Pulse rate/min.*	*Blood pressure mm. of Hg*	*Cardiac output % c*	*Blood flow cc./100 cc. min.*		*Body temp. ° C.*
											Fingers	*Toes*	
CONTROLS													
D. L.	8/30/48	27F	54	67	N.V.D.	21.8 ± 1.5	—	−4	−2 +8	−4	−1	−2	−0.2 R
H. M.	8/31/48	43M	86	75	N.V.D.	22.0 ± 2.0	—	0	+2 +2	+2	−4	−1	0.0 R
D. L.	9/1/48	30M	75	70	N.V.D.	21.0 ± 2.0	—	+2	+2 +3	±0	−1	−3	0.0 R
W. L.	9/2/48	27M	75	67	N.V.D.	21.0 ± 1.4	—	−5	0 −2	±0	−15	−5	−0.20
P. R.	9/7/48	29M	64	70	N.V.D.	21.5 ± 1.0	—	−4	+2 +2	—	−11	−3	−0.2 R
E. M.	9/9/48	41F	54	63	N.V.D.	22.0 ± 1.5	—	−8	0 +2	−3	−10	−2	0.0 R
Average							—	−3	+1 +3	−1	−7	−3	−0.1
C-5													
C. R.	3/21/50	25M	77	69	N.V.D.	23.0 ± 0.8	35	+20	+20 +14	+18	+25	+32	−0.4
R. B.	3/28/50	25M	66	67½	N.V.D.	23.1 ± 0.7	35	+26	+15 +10	+12	+15	+29	−0.9
J. B.	3/14/50	23M	66	66	N.V.D.	22.0 ± 1.0	35	+24	−5 +5	+10	+1	+1	−0.6
R. L.	4/8/50	24M	75	67	N.V.D.	23.2 ± 1.8	50	+20	−10 −10	+10	−1	0	−0.4
W. A.	4/17/50	26M	77	71	N.V.D.	24.0 ± 0.5	35	+8	0 0	+10	+23	0	−0.8
W. L.	4/19/50	26M	100	75	N.V.D.	23.5 ± 1.0	35	+32	0 0	+31	0	0	−0.3
J. O'B.	5/25/50	67M	80	67	A.S.	22.6 ± 1.4	35	+8	−20 −20	—	+20	+51	−0.8
J. O'B.	5/26/50	67M	80	67	A.S.	19.7 ± 0.6	35	—	—	—	0	+6	0

TABLE 1.—(*Continued*)

Subject	*Date*	*Age-Sex*	*Wt. (Kg.)*	*Ht. (inches)*	*Diagnosis*	*Room temp. ° C.*	*Dose (mg.)*	*Changes Induced*					
								Pulse rate/min.	*Blood pressure mm. of Hg*	*Cardiac output %*	*Blood flow cc./100 cc./min.*		*Body temp. ° C.*
											Fingers	*Toes*	
W. E.	5/29/50	51M	86.5	70	A.S.	22.0± 1.0	35	+8	−18/−5	—	+30	0	−0.3
Y. M.	7/20/50	42F	60	66	R.D.	23.0± 2.0	16	+30	−20/−5	—	+37	0	+0.2
A. D.	8/3/51	60M	65	69	A.S.	22.0± 0.7	30	−5	−60/−45	—	+29	0	0
H. W.	8/10/51	27M	65	68	A.S.	21.5± 1.5	40	+40	+20/+10	+42	−14	+16	0
L. H.	8/17/51	43M	90	68	V.V.	21.5± 1.5	35	+40	−60/−60	−4	+20	+6	0
J. N.	9/26/51	68M	60	61	D.C.D.	21.0± 1.5	30	−7	−30/−5	—	+27	+15	0
Average								+19	−13/−9	+29	+15	+11	−0.5
SKF 1700-A													
G. P.	8/2/51	68M	53	62	A.S.	23.0± 1.0	2.5	+32	−15/−10	—	−1	+2	−0.5
P. B.	8/6/51	45M	69	71	A.S.	23.0± 0.5	5	+20	+10/0	+8	+5	0	—
H. L.	8/8/51	57M	77	73	A.S.	23.0± 1.0	2	+12	−10/−15	—	−6	0	—
A. P.	8/10/51	28F	57	64	C.T.	23.5± 1.5	7.5	+60	+20/−5	—	−2	0	−0.5
J. C.	8/13/51	24M	65	68	N.V.D.	23.0± 1.0	7.5	+40	+25/−30	+53	+2	0	−0.2
W. B.	8/15/51	55M	93	78	A.S.	23.0± 0.5	7.5	+26	+15/+20	+58	−4	0	−0.3
G. P.	8/16/51	68M	53	62	A.S.	23.5± 0.5	7.5	+25	+25/+20	+78	−2	0	−0.2
H. S.	8/20/51	23M	82	72	N.V.D.	22.5± 0.5	10	+34	+30/−10	+69	−1	0	−0.3
H. N.	8/24/51	23M	70	72	N.V.D.	22.5± 0.5	15	+34	+50/−15	+55	0	0	−0.3
Average								+31	+17/−5	+74	−1	0	−0.3

BA 9295

M. B.	7/22/51	68M	81	69	N.V.D.	23.0± 0.6	50	+12	−15/−5	+14	+5	+7	−0.3
H. L.	7/26/51	57M	77	73	A.S.	23.0± 1.0	55	+16	−28/−10	—	+13	+14	−0.5
G. P.	8/2/51	68M	53	62	A.S.	23.0± 1.0	75	+14	−15/−5	—	0	0	−0.5
M. J.	8/29/51	40F	53	63	N.V.D.	23.0± 2.0	85	+30	+10/+15	+35	+1	+5	—
G. M.	12/6/51	62M	70	70	A.S.	23.0± 1.5	70	+20	+25/−10	+24	+18	+19	—
A. G.	1/9/52	64M	84	68	A.S.	23.0± 1.0	70	0	+30/+20	+10	−1	+1	—
G. T.	1/17/52	63M	66	66	A.S.	23.0± 1.0	70	−10	−25/−10	+13	+6	+5	—
J. L.	1/30/52	68M	69	68	N.V.D.	23.0± 1.0	80	+16	−35/−5	—	+37	+19	—
D. G.	2/6/52	75M	67	80	A.S.	23.0± 1.0	80	+10	−30/−5	—	—	+3	−0.2
T. T.	2/13/52	56F	71	64	N.V.D.	23.0± 1.0	75	+8	−55/−5	—	+14	+16	−0.8
Average								+14	−14/−2	+23	+10	+9	−0.5

— = Determination not made
V.V. = Varicose veins
R.D. = Raynaud's disease

A.S. = Peripheral arteriosclerosis
N.V.D. = No vascular disease
C.T. = Chronic thrombophlebitis with stasis ulcer

D.C.D. = Diffuse collagen disease

and severity. Others had no demonstrable lesions in the peripheral arterial bed. In 5 cases, healthy medical students were used to study the effects of C-5, and 2 medical students were used in the study of SKF-1700-A.

The subjects reported without having had food or medications for the 5 hours previously. They reclined, scantily clad in a hospital gown, on a ballistocardiographic table in a constant temperature room maintained at 23± 1°C. This temperature was chosen because it affords an adequate, yet not insuperable digital cutaneous vasoconstriction against which a drug can act.

Skin temperatures were measured with copper-constantan thermocouples taped lightly to the tips of the fingers and toes. Digital blood flow was estimated by a relationship previously established[7] and expressed in cc. per 100 cc. of digit per minute.

Pulse rates and blood pressures were measured by the standard methods at approximately 10-minute intervals. Cardiac output was measured by a ballistocardiograph of the Starr type[10] at approximately 20-minute intervals, and the results expressed in per cent deviation from normal. Oral temperatures were measured by a clinical thermometer held under the tongue for at least 5 minutes.

After the patients had rested for a period long enough to secure an adequate and steady control period for all phenomena measured, the drug was injected slowly over a period of 2 to 3 minutes into the antecubital vein. During administration of the drug, the dose was controlled by more frequent pulse and blood pressure recordings.

C-5 was administered in doses ranging from 15 to 50 mg. (0.28 to 0.75 mg./kg.). SKF-1700-A was administered in doses ranging from 5.0 to 15.0 mg. (0.07 to 0.20 mg./kg.). BA-9295 was administered in doses from 50 to 85 mg. (0.62 to 1.35 mg./kg.)

Control subjects, receiving only physiological saline parenterally, were 6 healthy adults ranging in age from 27 to 43 years. The results of the study of this group of normals have been reported previously[5]. Both control and experimental groups were studied under closely similar circumstances including season of the year.

Results. C-5. In 14 patients studied with this drug, the conspicuous changes observed were increased digital cutaneous blood flow, increased pulse rate, decreased blood pressure, and increased cardiac output.

Nine patients had increases in the digital cutaneous blood flow to the fingers, and seven to the toes. The mean increases in blood flow were 15 cc./100 cc. of digit/min. to the fingers and 11 cc. to the toes. These changes represent as much as 25 times the resting values and persisted from 40 to 200 minutes.

The pulse rate was increased in 8 of 13 patients, with a mean of 19 beats per minute. The systolic pressure was decreased in 7 of 13 patients, the diastolic in 4 of 13. The mean decrease in systolic pressure was 13 mm. of Hg, the mean decrease in diastolic, 9 mm. of Hg. In 2 cases the blood pressure was promptly and drastically reduced (-60/-45 and -60/-60) and the patients showed signs of peripheral circulatory collapse. One of these patients was a hypertensive (190/140) and the second a normotensive (130/85).

Cardiac output was promptly increased in 7 of 8 cases in which it was measured. The mean increase was 25%.

This drug appears to act widely on the vascular system with no preference for the digital cutaneous circulation.

SKF-1700-A. This drug had no significant effect on the digital cutaneous blood flow, while tending to accelerate the pulse rate severely, change the blood pressure variably, and increase the cardiac output to a marked degree. Other undesired effects were prominent.

Of 9 patients studied, only one had an increase in the digital cutaneous blood flow to the fingers, and none showed any increase in the flow to the toes.

The pulse rate was accelerated in all 9 subjects; the mean increase was 31 beats per minute. The systolic pressure was raised in 7, lowered in 2, and the diastolic pressure was low-

ered in 5, raised in 2. The mean increase in systolic pressure was 17 mm. Hg, the mean decrease in diastolic pressure 2 mm. Hg. Cardiac output was increased in all 6 subjects in whom it was measured; the mean increase was 74%. This large increase in cardiac output was to a considerable degree caused by an augmented stroke volume, as shown by the ballistocardiographic tracings. Thus, from the point of view of increasing blood flow to the skin, this drug was useless. It must increase flow primarily in areas other than the digital cutaneous.

Four of the 9 subjects had undesirable side effects. Two, both healthy medical students, had pallor, sweating, nervousness, mild tremor and frequent extrasystoles. One subject had a prolonged tachycardia for 3 hours after administration of the drug. One subject's cardiac rhythm was changed from that of a normal sinus to coupled auricular premature beats, as demonstrated by electrocardiogram.

BA-9295. Ten patients were studied with this drug, which tended to produce prompt, substantial and prolonged increases in the digital cutaneous blood flow, moderate increases in the pulse rate, moderate lowering of the systolic pressure, with almost no lowering of the diastolic pressure, and moderate increases in the cardiac output. No undesirable side effects were observed.

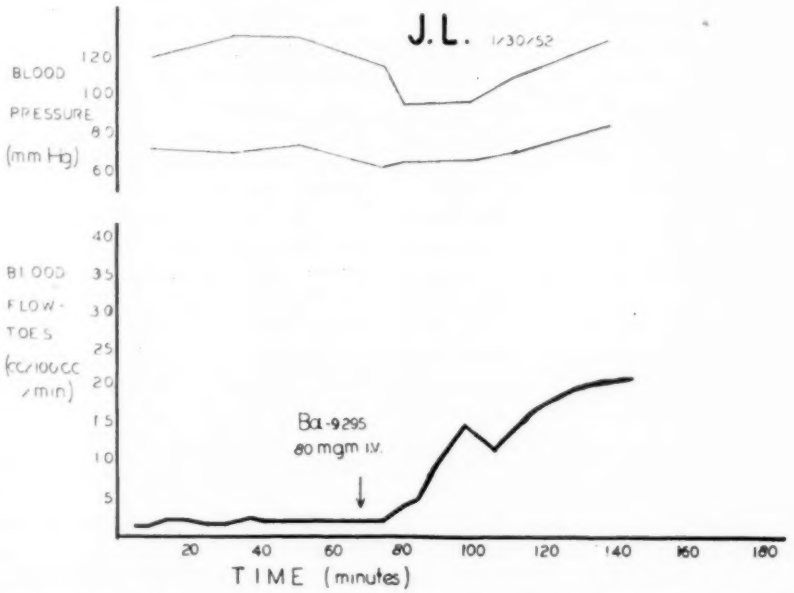


Fig. 1. — Graph of blood pressure and digital cutaneous blood flow in a 68-year-old male following administration of 80 mg. of BA-9295.

The digital cutaneous blood flow was increased significantly to the fingers of 6 patients, and to the toes of 8. The mean increase was 10 cc. to the fingers, and 9 cc. to the toes. These changes represent as great as 20-fold increases in the digital cutaneous blood flow. They persisted for from

30 to over 60 minutes following drug administration.

The pulse rate was increased in 7 patients; the mean increase was 14 beats per minute. The effect on blood pressure was variable. The systolic pressure was decreased in 7 subjects, the diastolic pressure decreased in 3. The mean change was decrease in systolic pressure of 14 mm. Hg, and a decrease in diastolic pressure of 2 mm. The cardiac output was increased in all 6 of the subjects in whom the measurement was obtained. The mean increase in cardiac output was 23%.

A typical result is demonstrated in Fig. 1.

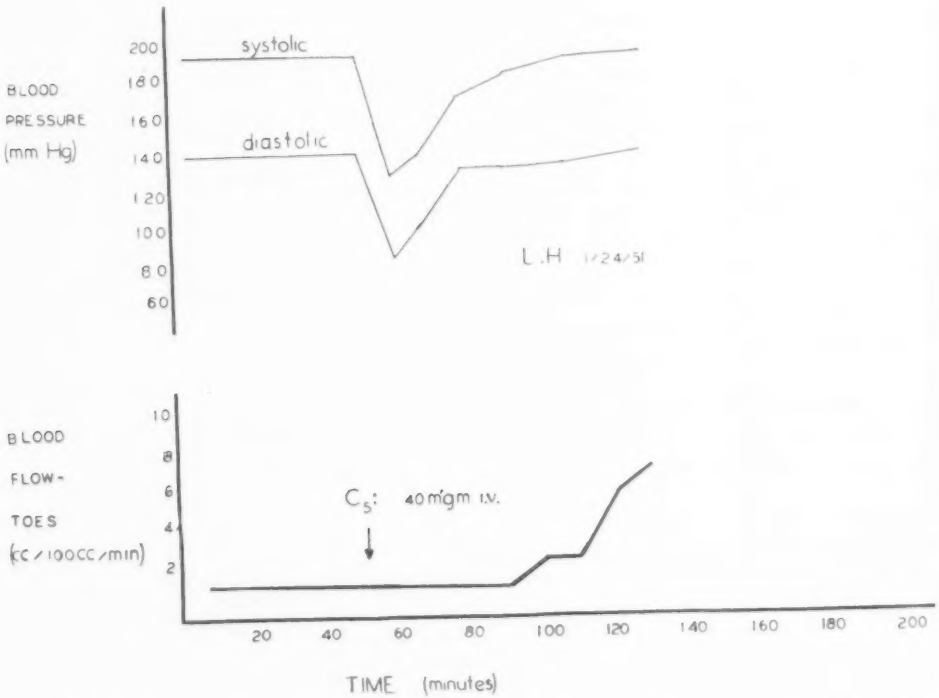


Fig. 2.—Graph of blood pressure and digital cutaneous blood flow in a 43-year-old male following administration of 40 mg. of C-5.

Discussion. An ideal agent in the treatment of peripheral arterial disease should increase the digital cutaneous blood flow without causing widespread changes in the rest of the circulation.

The first drug, C-5, demonstrated a definite ability to dilate the vessels of the skin of the extremities. It also was a powerful hypotensive agent. There was no way of predicting which of the 2 effects would obtain or predominate in the various individuals of our series. The tendency of this compound to produce profound and prompt hypotension demands careful observation of the patient and practically precludes its use on a long term, out-patient basis.

SKF-1700-A caused no vasodilatation in the skin of the extremities in doses that were arrhythmogenic in 4 of 9 patients, and increased the cardiac output consistently and to a marked

degree. The drop in diastolic pressure concurrent with an increased cardiac output and unchanged digital cutaneous blood flow indicates that vasodilatation occurred primarily elsewhere than in the skin, possibly in the splanchnic bed or muscles.

BA-9295 demonstrated a definite vasodilator effect which appears to be specific for the skin of the digits. This is evidenced by the slight drop in diastolic pressure and small increases in cardiac output accompanying its administration as well as significant increases in the digital cutaneous blood flow. These observations suggest that this drug could be of use in the treatment of peripheral arterial disease and deserves further study by oral administration.

One aspect of the concept of hemometakinesia, that is, that widespread vasodilatation can prevent an increase in the digital cutaneous blood flow, is shown in Fig. 2. Following injection of 40 mg. of C-5, there was a prompt fall in the blood pressure, with an unchanged digital cutaneous blood flow. As the pressure regained normal levels, the digital cutaneous blood increased slowly. This stands in contrast to the prompt increase in digital cutaneous blood flow seen following administration of C-5 in those cases in which only mild hypotension was observed, or following injection of BA-9295, which produced little lowering of the blood pressure and prompt increase in the blood flow to the skin of the digits. (See Fig. 1).

Summary. The effects of three vasodilator drugs used intravenously in human subjects were studied under constant environmental conditions by measuring digital cutaneous blood flow, cardiac output, pulse rate and blood pressure in order to determine their ability to produce selective vasodilatation in the skin of the digits.

C-5 increased the digital cutaneous blood flow in a significant number of subjects. It was also a powerful and unpredictable hypotensive agent, and increased the cardiac output of 7 of 8 subjects. We presume it dilates vessels in the rest of the body as well as in the skin and the relative degree of each differs with each person.

SKF-1700-A did not produce any significant increases in the digital cutaneous blood flow. It increased the cardiac output considerably. There were undesirable side effects, mostly of a sympathomimetic nature. Cardiac arrhythmias were prominent. We presume that it dilates vessels in the skin little or not at all in comparison with those elsewhere.

BA-9295 caused significant increases in the digital cutaneous blood flow in a majority of subjects studied. This was accompanied by only slight hypotension and small increases in the cardiac output. No undesirable side effects were observed. We presume that this drug causes vasodilatation predominately in skin and not much elsewhere; therefore, it may be a valuable drug in the treatment of peripheral arterial disease.

REFERENCES

1. Arnold, P., Goetz, R. H., and Rosenheim, M. L.: Lancet, **2**, 408, 1949.
2. Baikie, A. G., and Smith, J. R.: Lancet, **1**, 1144, 1952.
3. Bernsmeier, A., Esser, H., and Lorenz, W.: (In Press).
4. DeBakey, M. E., Burch, G. E., and Ray, T.: J. Michigan State Med. Soc.: **47**, 636, 1948.
5. Horwitz, O., Montgomery, H., Longaker, E. D., and Sayen, A.: Am. J. Med. Sci., **218**, 669, 1949.
6. Lottenbach, J.: Unpublished data.
7. Montgomery, H., Naide, M., and Freeman, N. E.: Am. Heart J., **21**, 780, 1941.
8. Montgomery, H.: Am. J. Med. Sci., **203**, 882, 1942.
9. Ostwald, E.: Med. Klinik, **23**, 733, 1950.
10. Starr, I., Rawson, A. J., Schroeder, H. A., and Joseph, N. R.: Am. J. Physiol., **127**, 1, 1939.

ORAL THERAPY WITH MERCUMATILIN (CUMERTILIN), A NEW MERCURIAL DIURETIC

By B. E. Pollock, Colonel, MC USA

AND

Francis W. Pruitt, Colonel, MC USA

(From the Medical Service, Letterman Army Hospital, San Francisco, California.)

Administration of mercurial diuretic drugs by the oral route would possess obvious advantages over the parenteral method. For this reason, each new mercurial diuretic introduced has been studied to determine its efficiency and safety for oral use, and reported in the literature[1,2,3,4,7]. Varying degrees of effectiveness of the several available mercurial diuretics have been shown to attend this method of administration. Toxic reactions, however, have tended generally to limit or prohibit its long-term clinical use.

Shapiro and Weiner[6] have reported mercumatilin to be a safe and effective new mercurial diuretic. During clinical use by parenteral administration they found no subjective or objective evidence of toxicity. Rose *et al.*[5] found the clinical effectiveness of this drug to be of a similar order to that of meralluride (Mercuhydrin) on parenteral administration; they also commented upon the lack of local or systemic toxicity in clinical use.

The present study was designed to determine the clinical feasibility of long-term use of mercumatilin tablets orally in the treatment of patients with congestive heart failure.

Method. Subjects for this study were selected from ambulant patients with cardiac disease regularly attending the cardiovascular clinic. Individuals were placed on oral mercumatilin therapy whenever it became apparent that adequate cardiac compensation could not be maintained by the use of full doses of drugs of the digitalis group supplemented in most cases by a low-salt diet. Such basic medication and dietary control were continued during the study. The program generally involved the use of parenteral mercurials to re-establish cardiac compensation, and the substitution of mercumatilin tablets orally to maintain compensation.

Dosage of mercumatilin varied from one tablet (67 mg. mercumatilin, equivalent to 20 mg. each of mercury and theophylline) 2 or 3 times a week to 5 tablets daily in different cases, depending upon clinical indications. The total dosage was commonly prescribed to be taken during the morning hours because several of the patients early in the study objected to increased diuresis at night. Rest periods during which the drug was omitted were not used.

Observations were made at the time of clinic visits for the presence of toxic effects and side reactions of the drug. The patients were studied for stomatitis, gingivitis, skin rashes, albuminuria and hematuria, and specific questions were asked regarding the occurrence of nausea, vomiting, abdominal cramps, muscular cramps, and diarrhea. The patients' lack of subjective symptoms, maintenance of "dry" weight, and absence of peripheral edema and pulmonary basal rales were considered as evidence for proper cardiac compensation.

Results. A total of 7,726 tablets of mercumatilin were administered orally to 20 patients during a total of 3,743 patient days for an average of about two tablets per patient per day during an average of 161 days (Table 1). Individuals under study have taken mercumatilin daily from a minimum period of 30 days to a maximum period of 504 days.

No evidence of significant toxic effects of the drug was found during the study. There were no reactions to diuresis, such as the low-salt syndrome.

Reactions were limited to looseness of bowels producing 2 to 4 movements daily. None of the patients complained of this symptom, but 3 of the patients had noted its presence when questioned. In one instance it had already cleared spontaneously after 2 or 3 days and without discontinuing the diuretic. No change was made in dosage, and the looseness of stools did not recur. In one case, the patient noted looseness of the bowel in the afternoon which persisted until administration of the 2 tablets of mercumatilin was changed to twice daily instead of one morning dose. In one case, the patient noted that he had loose stools following 3 tablets of the drug, but normal movements following 2 tablets. The one patient taking 5 tablets of the drug daily (equivalent to 100 mg. of mercury) noted no untoward effects, over a period of 399 days.

Addition of mercumatilin tablets to the regimen of all cases appeared clinically to be of value. Adequate cardiac compensation was maintained in 15 of the 20 cases with no further change in treatment. One patient was maintained in cardiac compensation for 180 days; apparent worsening of his cardiac condition thereafter required the addition of parenterally administered mercurials until his death 6 weeks later due to myocardial infarction. In 3 further instances, supplementary injections of mercurials were required from time to time to maintain compensation. In one case cardiac decompensation persisted during outpatient treatment and could be controlled only during periods of hospitalization, due undoubtedly to the poor cooperation of the patient.

Discussion. Mercumatilin appears from our study to be of clinical value in the management of the ambulant patient with heart disease who has been in cardiac decompensation. In the borderline case, and in the patient who has mild evidence of congestive failure, adequate control with oral Cumertilin therapy appears likely. The average patient who requires parenteral administration of mercurials will require fewer injections if oral therapy is used, and in some cases he will require none at all.

Lack of toxic effects renders the long-term use of oral tablets of Cumertilin safe. The absence of annoying side reactions permits patient acceptability, which is of practical importance since nausea, vomiting, and diarrhea have been the factors which made some of the older mercurial drugs clinically unacceptable for oral use.

A comparative assay of the effectiveness of oral and parenteral administration of mercumatilin did not form a part of this study. It was apparent during our work that the drug is clearly more effective by parenteral administration. It is not claimed as a result of this work that the oral use of mercumatilin will displace the parenteral route in the treatment of cases of marked congestive heart failure. The upper limit of tolerance for oral mercumatilin therapy has not been fully determined by this study, however, and further work to determine the practicability and value of larger dosage would appear to be in order.

Summary. Mercumatilin (Cumertilin) is a new and clinically effective mercurial diuretic. Tablets containing the equivalent of 20 mg. of mercury have been used in a study to determine their safety and value in the long-term treatment of patients with congestive heart failure. The drug was given to a total of 20 patients for periods varying from 30 to 504 days, for a total of 3,743 patient days and a total of 7,726 tablets, without evidence of toxicity and with no significant gastrointestinal reactions. The dosage used varied from less than one to 5 tablets daily. Addition of oral tablets of mercumatilin to the thera-

TABLE 1.—PATIENTS TREATED WITH LONG-TERM USE OF ORAL MERCURIAL DIURETIC (MERCUMATILIN)

Case No.	*Race*	*Sex*	*Age (yrs.)*	*Type of heart disease**	*Basic medication*	*Dosage of mercumatilin per day in tablets*	*No. of days administered*	*Total No. of tablets taken*	*Side reactions*	*Results*
1.	W	M	72	ASHD HCVD	Digitalis	1	504	504	Brief period of loose stools cleared spontaneously	Compensation maintained
2.	W	F	72	ASHD	Digitalis Low salt diet Amm. Chloride	2	355	710	None	Chronic congestive failure except while hospitalized
3.	W	M	76	ASHD HCVD	Digitalis Low salt diet	5	399	1995	None	Compensated
4.	W	M	54	ASHD	Digitalis Low salt diet	2	261	522	None	Compensated
5.	W	M	72	ASHD	Digitalis Low salt diet	2–3	249	648	Loose stool developed on dose of 3 tabs. per day, cleared when dose was reduced to 2 tabs.	Compensated for 218 days, then required parenteral supplement. Died of acute coronary occlusion
6.	W	F	58	RhHD	Digitalis Low salt diet	3	233	598	None	Compensated. Attempts to omit mercumatilin led to mild congestion which cleared when drug was reinstituted
7.	W	F	71	ASHD HCVD	Digitalis	(2–3 tabs per week)	222	114	None	Compensated
8.	W	M	60	ASHD	Digitalis Low salt diet	1	213	213	None	Compensated
9.	W	F	37	RhHD	Digitalis Low salt diet	2–3	149	312	Looseness of stools when pt. took 2 tabs. but not with 1 tab. twice daily	Occasional parenteral supplement needed

TABLE 1.—(*Continued*)

Case No.	*Race*	*Sex*	*Age (yrs.)*	*Type of heart disease*	*Basic medication*	*Dosage of mercumatilin per day in tablets*	*No. of days administered*	*Total No. of tablets taken*	*Side reactions*	*Results*
10.	W	M	80	ASHD	Digitalis Low salt diet	2	147	294	None	Compensated. Mercumatilin discontinued with no change in condition
11.	W	M	78	ASHD	Digitalis Low salt diet	1	146	146	None	Compensated. Mercumatilin discontinued with no change in condition
12.	W	M	52	ASHD	Digitalis Low salt diet	1–2	133	254	None	Compensated. Mercumatilin discontinued with no change in condition. Patient omitted digitalis and decompensated one month later
13.	W	F	70	HCVD	Digitalis Low salt diet	1	130	130	None	Compensated
14.	W	F	74	ASHD	Digitalis Low salt diet	2	125	250	None	Compensation maintained
15.	W	M	48	ASHD	Digitalis Low salt diet	1–3	119	223	None	Occasional parenteral mercurial supplement required
16.	W	F	66	RhHD	Digitalis Low salt diet	2–3	119	293	None	Compensation maintained
17.	W	F	67	ASHD	Digitalis	2	90	180	None	Compensation maintained
18.	W	F	56	RhHD	Digitalis Low salt diet	2	77	154	None	Compensation maintained
19.	W	M	64	ASHD	Digitalis Low salt diet Parenteral mercurials	3	42	126	None	Supplementary parenteral mercurials required twice weekly
20.	W	M	61	ASHD	Digitalis Low salt diet	2	30	60	None	Compensation maintained

*ASHD Arteriosclerotic heart disease HCVD Hypertensive cardiovascular disease RhHD Rheumatic heart disease

peutic regimen maintained cardiac compensation in 15 out of 20 cases in which digitalization and low-salt diet had become inadequate. Supplements of parenteral mercurials were required in the remaining 5 cases. Mercumatilin appears to be a safe and clinically useful drug for oral use in the management of congestive heart failure.

ADDENDUM: Since preparation of this paper the study has been continued. It now embraces 25 patients treated over a period of 77 to 658 days, for a total of 5,750 patient days and a total of 11,130 tablets. Results remain essentially as reported above. In one case skin rash developed after mercumatilin administration for 85 days (170 tablets), cleared on withdrawal of all medication, and recurred after a single injection of mercaptomerin sodium.

Appreciation is expressed for supplies of Cumertilin tablets provided by Dr. Samuel M. Gordon of Endo Products, Inc.

REFERENCES

1. **Batterman, R. C., DeGraff, A. C.,** and **Rose, O. A.**: Am. Heart J., **21**, 98, 1941.
2. **Derow, H. A.,** and **Wolff, L.**: Am. J. Med., **3**, 693, 1947.
3. **Greiner, T., Gold, H., Palumbo, F., Warshaw, L., Weaver, J., Marsh, R., Mathes, S.,** and **Kwit, N. T.**: Proc. Soc. Exper. Biol. & Med., **80**, 117, 1952.
4. **Jendrassik, E.**: Deutsch. Arch. f. klin. Med., **38**, 499, 1886.
5. **Rose, O. A., Lhowe, J.,** and **Batterman, R. C.**: Am. Heart J., **40**, 779, 1950.
6. **Shapiro, S.,** and **Weiner, M.**: J. Lab. & Clin. Med., **36**, 224, 1950.
7. **Stroud, W. D., Laplace, L. B., Wagner, J. A.,** and **Miller, I. B.**: Pennsylvania Med. J., **53**, 953, 1950.

OCCUPATION AS A FACTOR IN THE COMMUNITY HEALTH HAZARDS OF AIR POLLUTION

By C. A. Mills, M.D.
PROFESSOR OF EXPERIMENTAL MEDICINE

(From the University of Cincinnati, Cincinnati, Ohio)

In our efforts further to clarify the community health hazards of urban air pollution[1,2], we have now extended our Chicago study to cover a comparison of pneumonia and respiratory tract cancer death rates in the city's contrasting cleanest and dirtiest areas on an occupational basis. Our findings are clear-cut and striking, indicating a sharp increase in pneumonia and respiratory tract cancer hazards among those workers most exposed to outdoor atmospheric conditions in the city's most polluted districts.

Previous recognition has been given to the existence of such hazards among specific groups of employees in certain industries carrying known exposure dangers, such as chromate workers, hot tar handlers and others. No such studies have been made on whole population groups, however, in an effort to see whether certain occupational segments of the general population living in a badly polluted outdoor atmosphere are subjected to more severe respiratory hazards than a similar occupational group living in a clean area. Graham and Wynder[3] have said, for instance, that "city dusts and fumes cannot account for the increased incidence of lung cancer," but their supporting data included only a comparison of lung cancer prevalence with that for other (non-cancerous) diseases of the chest among urban hospitalized populations. It should be evident that any non-specific atmospheric irritants leading to lung cancer might also be likely to lead to an increased incidence of other pulmonary troubles such as pneumonia, tuberculosis, emphysema, fibrosis, and the like.

In this expansion of our Chicago studies, we have chosen deaths from the pneumonias and cancers of the respiratory system as the two most obvious expressions of chronic nonspecific irritational influences on the respiratory system. In all of our air pollution studies thus far these two have shown a similar tendency to increase in severity with increasing degrees of locally prevailing air pollution. Our present analysis now carries the study one step further and shows that those occupational groups with the greatest degrees of exposure to prevailing outdoor pollution exhibit the sharpest rise in death rates for both pneumonia and respiratory tract cancer in the city's dirtiest districts as contrasted to the city's cleanest areas.

The accompanying table of data illustrates these points very clearly indeed. The "laborers" occupational classification includes largely outdoor common laborers and thus represents the city's occupational group with greatest exposure to prevailing outdoor air conditions. This occupational group would also be likely to be the most poorly housed and lowest in other aspects of the socio-economic classification. It would be expected that this group would show highest pneumonia death rates, according to the usual public health concepts, but the close similarity between this group's pneumonia rates and those for respiratory

tract cancers carries significance of a quite different order.

It is evident from the rates shown that "laborers" have death rates for both diseases 2.5 to 3.5 times higher than the "professional" group in both clean and dirty districts. The "laborer" respiratory tract cancer rate is almost twice as high in dirty as in clean districts and its pneumonia death rate almost 3 times as high. In all categories the "protective and other services" group ranks second highest, but still considerably less afflicted than the "laborer" group.

It would be very desirable to have these deaths regrouped on the basis of employment location in addition to place of residence, but such a regrouping would involve an individual case-history survey quite beyond our meager research funds available. It would seem likely that such a regrouping would still further increase the evidence of respiratory hazards outdoor workers face from breathing polluted air. It may also be significant that it is the physical worker expending the greatest amount of energy and consequently breathing the largest volumes of the dirty air who faces the greatest respiratory hazards.

TABLE 1.—DEATH RATES FOR PNEUMONIA AND RESPIRATORY TRACT CANCER BY OCCUPATION

(CHICAGO'S CLEANEST AND DIRTIEST AREAS, 1944–5–6, MALES ONLY)

	Buccal and Respiratory Tract Cancers					
	Community Areas 1–4, 9–21, 72–5 (Clean)			*Community Areas 8, 26–8, 31–9, 59–61 (Dirty)*		
Occupational Groups	*Pop. at risk census of (1940+1950)÷2)*	*Deaths of 1944–5–6*	*Annual rate per 100,000 pop.*	*Pop. at risk census of (1940+1950)÷2*	*Deaths of 1944–5–6*	*Annual rate per 100,000 pop.*
Professional, etc.	25890	13	16.7	11986	14	39.0
Proprietors, etc.	35610	40	37.4	15273	24	52.4
Clerical, etc.	58214	68	38.9	32819	39	39.6
Craftsmen, etc. Semi-Skilled, etc.	94798	127	44.7	87765	89	33.8
Service Workers (except household)	16414	27	54.8	32062	50	52.0
Laborers	8255	15	60.6	33204	106	106.4
	All Pneumonias					
Occupational Groups						
Professional, etc.	25890	14	18.0	11986	16	44.5
Proprietors, etc.	35610	21	19.7	15273	21	45.9
Clerical, etc.	58214	42	24.0	32819	47	47.7
Craftsmen, etc. Semi-Skilled, etc.	94798	84	29.5	87765	124	47.1
Service Workers (except household)	16414	18	36.5	32062	82	85.2
Laborers	8255	14	56.5	33204	164	164.5

N. B.: Assistance of Public Health Division of Chicago Board of Health in the preparing and statistical sorting of punch cards is gratefully acknowledged.

Conclusion. While we would not say that urban air pollution is responsible for "*the* increased incidence of lung cancer," it does seem to be *one* significant factor in this increase. Any factor associated with a doubling of the lung cancer rate is certainly significant, especially when its doubling can scarcely be linked to housing, nutritional state, socio-economic status or any other environmental factor except irritants in the air breathed.

REFERENCES

1. **Mills, C. A.**, and **Porter, M. M.**: Occup. Med., **5**, 614, 1948.
2. **Mills, C. A.**: Am. J. Med. Sci., **224**, 403, 1952.
3. **Wynder, E. L.**, and **Graham, E. A.**: Arch. Indust. Hyg. & Occup. Med., **4**, 221, 1951.

SOME EFFECTS OF NITROGEN MUSTARD AND TRIETHYLENE MELAMINE* IN ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS**

By Robert J. Rohn, M.D.
ASSISTANT PROFESSOR OF MEDICINE

AND

William H. Bond, M.D.
INSTRUCTOR IN MEDICINE

(From the Department of Medicine, Division of Hematology, Indiana University Medical Center, Indianapolis, Indiana)

Since the middle of the 19th century when acute disseminated lupus erythematosus was described by Hebra[9], Casenave[1], and Kaposi[10] it has been recognized as a progressive disorder which usually terminates fatally. Although a multiplicity of drugs was employed in the treatment of this condition, therapeutically induced remissions of any significant duration were rarely observed. With pituitary adrenocorticotropic hormone (ACTH) and cortisone, however, it was found that remissions could be obtained with a fair degree of regularity, and on maintenance therapy with these agents, remissions sometimes persisted for relatively long periods of time[5,6,18].

Certain difficulties are encountered in treating acute disseminated lupus when very large doses are employed crisis[5], dangerously large amounts of cortico-steroids must be used. Even when very large does are employed they do not always prove effective during such critical periods. On moderate and sometimes small dosage schedules, electrolyte imbalance, complicating secondary infections, and mental disturbances occasionally negate the beneficial effect which can be obtained. A further disadvantage is the considerable expense which prolonged therapy with ACTH and cortisone entails.

Because of these considerations we became interested in the investigation of other therapeutic agents which might be employed when corticosteroid therapy was ineffective or contraindicated.

We were aware of the effect of nitrogen mustard in sensitization reactions[3], asthma[15,19], glomerulonephritis[2,14], rheumatoid arthritis[4,17] uveitis[13], and atopic eczema[19]. As acute disseminated lupus erythematosus is also regarded as a sensitization disorder[7,11], we thought it might be of interest to make a clinical trial of nitrogen mustard therapy in some of our patients with this disease. If nitrogen mustard therapy proved effective we were also interested in determining whether the effect was mediated through the pituitary-adrenal axis as had been suggested by Salomon[15] and Shutkin[17] or whether it had some differing mechanism of action. After the original presentation of this study** we found that a similar therapeutic trial had been reported previously by

* The triethylene melamine used in this study was provided by Dr. J. M. Ruegsegger of Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

** Presented at the Tenth Annual Meeting of the Midwestern Section of The American Federation for Clinical Research, Chicago, Illinois, November 6, 1952.

TABLE 1.—SUMMARY OF INDIVIDUAL RESPONSE TO VARIOUS AGENTS USED IN THE TREATMENT OF ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

Pt.	*Diagnosis*	*Clinical Manifestations*	*Remission on HN_2*	*Remission on TEM*	*Remission on ACTH*	*Remission on Combined ACTH and HN_2*	*Remission on Combined ACTH and TEM Therapy*
1. B. S. 27WF	Acute Disseminated Lupus Erythematosus a. Clinical features b. "L.E." cells in marrow	Arthropathy Skin rash-gen. Dysphagia Abdominal pain	17 days	13 days	‡10 days	17 days	10+ days
2. I. B. 28WF	Acute Disseminated Lupus Erythematosus a. Clinical features b. "L.E." cells in bone marrow c. Skin biopsy Idiopathic Epilepsy E.E.G. Tuberculosis-Sputum positive Secondary Hemolytic Anemia	Fever Anemia (Hemolytic) Skin Rash Leg Pain	* 44 days †217 days ‡ 21+ days				
3. O. D. 53CF	Acute Disseminated Lupus Erythematosus a. Clinical features b. "L.E." cells in bone marrow	Fatigue Fever Epigastric Pain Rash	20 days	6+ days	14 days		
4. E. C. 65WF	Acute Disseminated Lupus Erythematosus a. Clinical features b. "L.E." cells in bone marrow	Rash Fever Disorientation	No Response		No Response		
5. G. K. 49WM	Acute Disseminated Lupus Erythematosus a. Clinical features b. "L.E." cells in bone marrow	Arthropathy Fever Abdominal Pain Dysphagia	No Response		*300 days †205+ days		

* Denotes 1st remission
† Denotes 2nd remission
‡ Denotes 3rd remission
+ Denotes persisting remission at time of last examination

Mario Plaza de Los Reyes and Juan Monsalve y Americo Antillo[12] in 2 of their patients with acute disseminated lupus erythematosus.

Five patients with proven acute disseminated lupus erythematosus were treated with nitrogen mustard and, in some instances, with triethylene melamine. In 4 of the 5 patients this therapy was contrasted with corticosteroid therapy. The patients, methods of diagnosis, and duration of remissions are summarized in Table 1. Brief case reports of the patients treated follow.

Case Reports. CASE 1. B.S. This 25-year old white lady was admitted to the Indiana University Medical Center on May 1, 1952, complaining of weakness, migratory joint pains, skin rash, and episodes of epigastric pain often accompanied by vomiting. There was a past history of an attack of pleurisy one year prior to admission. Physical examination revealed the following positive findings: Temperature of 99.2° F., a maculopapular skin eruption covering extremities and trunk, and slight cervical lymphadenopathy. Laboratory findings were as follows: Urinalysis was normal. The serologic test for syphilis was negative. The total non-protein nitrogen was 33 mg. per 100 cc. The fasting blood sugar was 86 mg. per 100 cc. Total serum proteins were 7.40 gm. per 100 cc. with albumin of 3.45 gm. and globulin of 3.95 gm. A blood culture was negative. The hemoglobin was 12.1 gm. per 100 cc. The erythrocyte count was 4.44 million per c.mm. Leukocytes numbered 3800 per c. mm., with the differential count revealing 85% neutrophils, 2% metamyelocytes, 8% lymphocytes, and 5% monocytes. Reticulocytes were 1.1%. The platelet count was 799,200 per c. mm. A bone marrow preparation revealed 20.5% typical "L.E." cells. Roentgenograms of the chest, joints, and gastrointestinal tract were all normal. The patient was treated with nitrogen mustard receiving a total dosage of 0.4 mg./kg. of body weight. A complete remission occurred which lasted a total of 17 days. The patient was readmitted to the hospital on June 22, 1952, with a recurrence of all symptoms, and especially marked epigastric and substernal pain with vomiting. On this admission she received a course of triethylene melamine consisting of 5 mg. orally on three successive days. A remission of 13-days' duration was obtained. The third hospital admission was on August 4, 1952, at which time there was again recurrence of all symptoms. Because of the brevity of the remissions obtained with nitrogen mustard and triethylene melamine it was decided to treat this patient with adrenocorticotropic hormone (ACTH). She responded well to 60 units of ACTH daily and complete remission was obtained. Patient was carried on maintenance doses of ACTH and remained in remission for 210 days at the end of which time there was recurrence of rash, epigastric and joint pains. The fourth hospital admission was on February 23, 1953. She was given ACTH in doses of 60 mg. daily. With no clinical response evident after 15 days of therapy she was given a total dosage of 0.2 mg./kg. of body weight of nitrogen mustard concomitantly with the ACTH. On this combined therapy a complete remission was obtained which lasted 17 days. On April 2, 1953, because of another relapse the patient was given 10 mg. of triethylene melamine over a 2 days' period in addition to 60 units daily of ACTH. On this combined therapy there was complete disappearance of symptoms in 4 days. At the end of 10 days she had a mild recurrence of symptoms and at the time of this writing she is on a program of combined daily ACTH in 60 mg. doses with triethylene melamine 5 mg. per week. Significant laboratory and clinical findings before and after each course of therapy are summarized in Table 2.

CASE 2. I.B. This 28-year old white lady was admitted to the Indiana University Medical Center for the first time on May 16, 1952, because of a purpuric rash, irregular fever, and leg pains of 3 weeks' duration. She had been a patient at the Indiana Village for Epileptics since the age of 12 years, and had been hospitalized there since August, 1951, for pulmonary tuberculosis and had received therapy with streptomycin and para-aminosalicylic acid. Positive physical findings included temperature of 102.8° F. and a blotchy purple colored skin eruption scattered over the upper and to a greater extent the lower extremities. Joints showed no abnormalities. Laboratory findings were as follows: Urinalysis was normal. The serology was negative. Sputum was positive for tubercle bacilli. Total serum proteins were 7.40 gm. per 100 cc. with albumin of 3.45 gm. and globulin of 3.95 gm. Hemoglobin was 5.5 gm. per 100 cc. Erythrocytes numbered 1.94 million per c. mm. The total white count was 14,250 per c. mm. with a differential of 6% neutrophils, 18% eosinophils, 3% neutrophilic "C" myelo-

* Denotes 1st remission
† Denotes 2nd remission
‡ Denotes 3rd remission
‡ Denotes persisting remission at time of last examination

TABLE 2.—SUMMARY OF LABORATORY AND CLINICAL RESPONSE TO NITROGEN MUSTARD, TRIETHYLENE MELAMINE AND ACTH THERAPY IN PATIENTS G. K. AND B. S.

	Before HN_2		*After HN_2*		*Before TEM*		*After TEM*		*After ACTH*	
Patient	*G. K.*	*B. S.*	*G. K.*	*B. S.*	*G. K.*	*B. S.*	*G. K.*	*B. S.*	*G. K.*	*B. S.*
17-Ketosteroid 24 hour Excretion	2.9 mg.		9.9 mg.			4.0 mg.		6.8 mg.	22.6 mg.	3.9 mg.
11-Oxysteroid 24 hour Excretion	1.6 mg.		3.0 mg.			1.8 mg.		2.1 mg.	5.6 mg.	1.2 mg.
Uric Acid-Creatinine Ratio	4:1		Slight Increase			2.1:1		4.1:1		0.4:1
Total Serum Protein	5.6 gm.	7.4 gm.		7.4 gm.		7.2 gm.		7.2 gm.		8.0 gm.
Serum Albumin	3.9 gm.	3.45 gm.	Unchanged	3.26 gm.		3.71 gm.		3.58 gm.	Unchanged	3.9 gm.
Serum Globulin	1.7 gm.	3.95 gm.		4.14 gm.		3.49 gm.		3.62 gm.		4.1 gm.
Erythrocyte Sedimentation Rate (Normal 0.4)	1.1	0.9	0.7	1.4		1.4		1.45		1.3
Total White Blood Count	5800 per c.mm.	3800 per c.mm.	1950 per c.mm.	2150 per c.mm.		2850 per c.mm.		1450 per c.mm.	5500 per c.mm.	6300 per c.mm.
Quantitative Marrow "L.E." Cell Count	14.5%	20.5%	12.5%	7.0%		14.0%		4.0%	9.5%	5.5%
Clinical										
Fever	102.4° F.	99.2° F.	102.4° F.	98.6° F.		100.4° F.		98.8° F.	98.6° F.	98.6° F.
Arthropathy	Marked Limitation	Swollen Red	Marked Limitation	Complete Recovery 2 days		Swollen Red Limitaton		Complete Recovery 8 days	Good Recovery	Complete Recovery 4 days
Skin Eruption		Gen. Macular Erythema		Complete Recovery 2 days		Gen. Macular Erythema		Complete Recovery 2 days		Complete Recovery 10 days
Dysphagia	Marked		Marked			Marked		Complete Recovery 2 days	Marked Improve-ment	Complete Recovery 7 days

TABLE 3.—SUMMARY OF LABORATORY AND CLINICAL RESPONSE TO NITROGEN MUSTARD THERAPY IN PATIENT I. B.

I. B. 28 WF	*Before 1st Course HN_2*	*After 1st Course HN_2 (0.2 mg./Kg.)*	*Before 2nd Course HN_2*	*After 2nd Course HN_2 (0.2 mg./Kg.)*	*Before 3rd Course HN_2*	*After 3rd Course HN_2 (0.3 mg./Kg.)*
Total Red Count	1.94 million per c.mm.	2.89 million per c.mm.	2.42 million per c.mm.	3.80 million per c.mm.	4.37 million per c.mm.	4.07 million per c.mm.
Hemoglobin	5.5 gm.	8.8 gm.	9.3 gm.	11.8 gm.	14.5 gm.	13.1 gm.
Reticulocytes	46.3%	10.3%	1.9%	1.5%	0.9%	1.5%
Total White Blood Count	14,250/c.mm.	3700/c.mm.	3250/c.mm.	9800/c.mm.	4200/c.mm.	4100/c.mm.
Erythrocyte Sedimentation Rate (Normal 0.4)	0.25	0.1	0.1	0.2	0.2	0.1
Quantitative Bone Marrow L.E. Cells	9%	1.0%	14.5%	1.0%	6.5%	5.0%
Auto Immune Antibodies (Trypsinized Cells)	Positive 1:8 Dilution	Positive Undiluted	Positive Undiluted	Positive 1:2 Dilution	Positive 1:2 Dilution	Positive 1:2 Dilution
Auto Immune Antibodies (Developing Serum)	Positive 1:512 Dilution	Positive 1:16 Dilution	Negative	Positive Undiluted	Negative	Positive Undiluted
Cold Agglutinins	Positive 1:128 Dilution	Positive 1:16 Dilution	Positive 1:16 Dilution	Positive 1:16 Dilution	Positive 1:8 Dilution	Positive 1:16 Dilution
Osmotic Fragility	0.618–0.341	0.439–0.341	0.439–0.341	0.471–0.319	0.471–0.282	0.450–0.366
Clinical						
Fever	102.6° F.	98.6° F.	99.8° F.	98.6° F.	99.6° F.	98.8° F.
Skin Lesions	Vesicular Hemorrhagic	Partially Clear 3 days	Vesicular Hemorrhagic	Disappeared in 8 days	None	None
Leg Pain	Severe Generalized	Recovered in 2 days	Severe Generalized	Recovery in 2 days	None	None
Pleuritic Pain	None	None	None	None	Moderate	Disappeared 3 days

cytes, 2% metamyelocytes, 15% lymphocytes, and 6% monocytes. Total platelet count was 269,660 per c. mm. There were 46.3% reticulocytes and 6 nucleated red cells for every 100 white cells counted. Autoagglutination of red cells was marked. The osmotic fragility of the erythocytes was left-shifted, with hemolysis beginning at 0.618 and complete at 0.341 saline concentration. Cold agglutinins were positive in a 1:128 dilution. Developing serum antibodies were positive in a 1:512 dilution and trypsinized cell antibodies were positive in a 1:8 dilution. Bone marrow examination revealed 14.5% typical "L.E." cells. A skin biopsy revealed findings compatible with a diagnosis of disseminated lupus erythematosus. Chest Roentgen-ray examination showed strand-like infiltrative densities extending laterally and superiorly from the right hilum. Gastrointestinal tract roentgenograms were normal. On the basis of all these findings a diagnosis of acute disseminated lupus erythematosus with an acquired hemolytic anemia was made. Because of the presence of active pulmonary tuberculosis it was felt that corticosteroid therapy was contraindicated, and a trial of nitrogen mustard therapy was decided upon. She received a total dosage of 0.2 mg./kg. of body weight of nitrogen mustard. Following this therapy she had a complete remission for 44 days. She was readmitted to the hospital on July 17, 1952, in relapse with recurrence of all symptoms except the hemolytic anemia. A second course of nitrogen mustard of 0.2 mg./kg. of body weight was given and a second remission obtained which lasted 217 days. The third hospital admission was on March 5, 1953, at which time the patient was again in relapse, with malaise and pleuritic pain being the principal symptoms. She received a third course of nitrogen mustard of 0.3 mg./kg. of body weight and a remission was again obtained. Chest films showed no change in the pulmonary tuberculous lesions. At the time of this writing the patient is still in remission which is now of 21 days' duration. Laboratory and clinical findings before and after each course of nitrogen mustard are summarized in Table 3.

CASE 3. O.D. This 53-year old colored female was admitted to the medical service of the Indiana University Medical Center on April 11, 1952, because of fatigue, weakness, and fever of 10 months' duration. During this period she had received 7 blood transfusions. Physical examination revealed the following positive findings: Marked debilitation and dehydration, temperature of 101.8° F., a generalized reddish-purple macular skin eruption which showed a butterfly configuration over the cheeks, dulness to percussion and diminished breath sounds over both lung bases, liver palpable 10 cm. below right costal border, and uterine masses thought to be calcified fibroid tumors, and slight pretibial edema. Laboratory findings were as follows: Urinaylsis showed a trace of albumin and many pus cells. Urine culture yielded *E. coli* and *A. aerogenes*. The non-protein nitrogen was 39 mg. per 100 cc. Blood sugar was 115 mg. per 100 cc. Total serum proteins were 6.80 gm. per 100 cc. with an albumin of 3.26 gm. and a globulin of 3.54 gm. The serologic test for syphilis was negative. Hemoglobin was 5.3 gm. per 100 cc. Erythrocytes numbered 2.22 million per c. mm. The leukocyte count was 13,450 per c. mm. The differential showed 62% neutrophils, 2% "L.E." cells, 10% "C" myelocytes, 2% metamyelocytes, 12% lymphocytes, and 12% monocytes. Reticulocytes were 6.1%. The platelet count was 455,000 per c. mm. Bone marrow was aspirated with difficulty and seemed tightly packed; the drops of aspirate obtained showed many typical "L.E." cells. Chest films revealed pulmonary congestion at both bases. Gastrointestinal tract roentgenograms were normal. Patient was treated with ACTH receiving 100 to 160 mg. per day for 6 weeks followed by cortisone for 2 weeks. In addition, she received specific treatment for congestive failure and the urinary tract infection. On this regimen the patient showed only partial improvement. The temperature was normal for 14 days and the rash partially faded. However, while on corticosteroid therapy she developed marked mental confusion, had convulsive seizures, developed hyperglycemia and mild hypertension, and had gradual return of fever. Because of failure to obtain complete control of her disease and because of the undesirable side effects described above, corticosteroid therapy was gradually discontinued. She was then given a course of nitrogen mustard therapy of 0.3 mg./kg. of body weight following which there was a return of temperature to normal, and clearing of the rash with increased strength and appetite. This remission lasted 20 days following which she was given a course of triethylene melamine consisting of 2 mg. daily doses for a total of 14 mg. After the course of triethylene melamine she had another remission similar to the first. She was discharged from the hospital to a nursing home on August 10, 1952, after she had been symptom-free for 6 days. No follow-up on this patient could be obtained.

CASE 4. E.C. This 60-year old white lady was admitted to the Indiana University Medical Center on May 9, 1952, because of widespread rash, mental confusion, and high fever of a week's duration. Positive physical findings included fever of 102.4° F., emaciation, disorientation, generalized maculopapular skin eruption, and moderate cervical lymphadenopathy. Laboratory findings were as follows: Urinalysis was normal. Blood culture was negative. The total serum proteins were 6.40 gm. per 100 cc. with an albumin of 2.81 gm. and a globulin of 3.59 gm. The nonprotein nitrogen was 32 mg. per 100 cc. The hemoglobin was 9.3 gm. per 100 cc. Erythrocytes numbered 3.12 million per c. mm. The white blood cell count was 7300 per c. mm. Differential showed 76% neutrophils, 1% basophils, 10% lymphocytes, and 13% monocytes. Autoagglutination was marked. Reticulocytes were 1.5%. The platelet count was 1,534,000 per c. mm. Bone marrow examination revealed 19% typical "L.E." cells. She received a course of nitrogen mustard 0.3 mg./kg. body weight, which was without any discernible effect. She was then given ACTH which was also without effect on the course of her disease which was steadily downhill with death occurring on June 22, 1952.

CASE 5. G.K. This 49-year old white male was first admitted to the Indiana University Medical Center on July 14, 1951, because of bleeding from tooth sockets following extraction of several teeth. Physical findings of fever, gingival bleeding and purpuric rash suggested a blood dyscrasia. However, bone marrow examination revealed 9.5% typical "L.E." cells. He was placed on ACTH therapy and became asymptomatic on doses of 60 to 100 mg. daily. While on this drug he developed an acute psychotic episode, and difficulty in maintaining proper electrolyte balance was encountered. Eventually, a complete remission was obtained with disappearance of "L.E." cells from the marrow. He remained in remission for 300 days during which period he received no medication of any sort. The second hospital admission was on June 23, 1952, at which time he complained of marked dysphagia, and pain in hands and knees. Positive physical findings were limited to fever of 102.4° F., marked limitation of motion in the interphalangeal joints and knees, and slight epigastric tenderness. Bone marrow examination revealed 14.5% "L.E." cells. Because of the prolonged psychotic episode he had had on previous ACTH therapy it was decided to give the patient a trial of nitrogen mustard therapy. He received a total dose of 0.3 mg./kg. body weight of this drug. This course of therapy appeared to have no significant effect on the clinical course of the disease, and bone marrow examination after therapy revealed moderate hypocellularity with still 12.5% "L.E." cells. He was again placed on ACTH therapy and there was a gradual disappearance of symptoms. The patient is still in remission, which has been in progress for 205 days at the time of this writing. He is receiving maintenance doses of ACTH ranging from 10 to 20 mg. daily. Laboratory and clinical findings before and after therapy are briefly summarized in Table 2.

Results. As can be seen in Table 1, we were able to obtain remissions of varying degree in 3 of the 5 patients given nitrogen mustard and triethylene melamine. The length of remissions varied from a minimum of 6 days to a maximum of 217 days. This contrasted with minimum ACTH induced remission of 14 days and a maximum of 300 days.

In patient No. 4 (Table 1) no response was observed following therapy with either ACTH or nitrogen mustard. In patient No. 3 (Table 1) ACTH was employed initially. After a remission of 14 days' duration this patient became psychotic and disturbed, and both ACTH and cortisone therapy had to be discontinued. She was then started on nitrogen mustard therapy and obtained a remission of 20 days. Upon relapse she was started on triethylene melamine therapy. After remission had been obtained for 6 days she was released from the hospital. As she failed to meet her return appointment the duration of this remission could not accurately be determined.

In patient No. 1 (Table 1) excellent but brief remissions were observed following nitrogen mustard and triethylene melamine therapy. On ACTH an excellent, prolonged remission of 210 days was observed. At the end of this period she began to note recurrence of her previous symptomatology in spite

of continued usual maintenance therapy. Her ACTH was increased from 20 to 60 mg. per day with no significant improvement. It was decided to continue ACTH therapy at a 60 mg. daily dosage level and supplement it with nitrogen mustard therapy. She was accordingly given 0.3 mg./kg. body weight of nitrogen mustard in divided dosage with prompt disappearance of her symptoms. Her remission persisted for 17 days at which time she

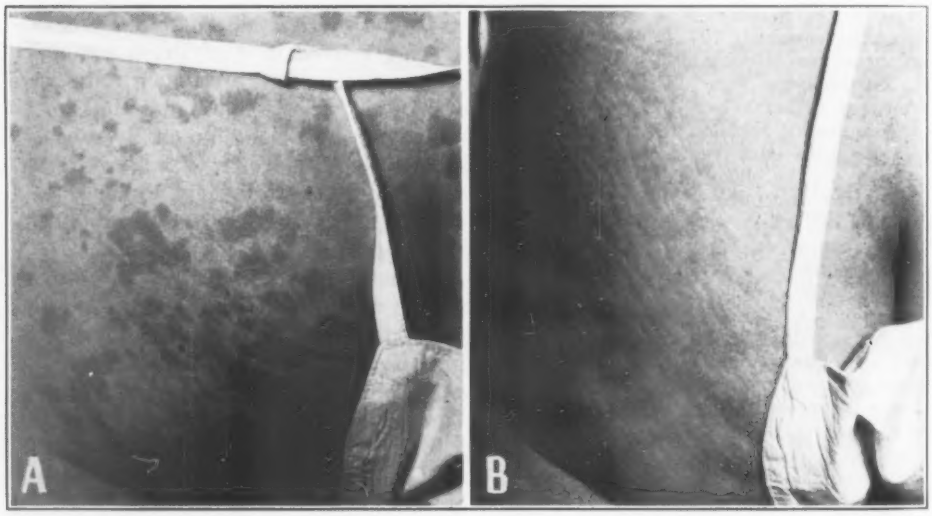


Fig. 1.— Response to nitrogen mustard therapy of skin lesions in patient No. 1 (Table 1). (A) Before therapy. (B) Two days after nitrogen mustard therapy.

observed, in spite of continuing ACTH therapy, a recurrence of some of her previous symptomatology. She was then given 10 mg. of triethylene melamine. Within 4 days she became asymptomatic. At the end of 10 days there was mild reactivation of her disease process and a program of 60 mg. daily ACTH combined with 5 mg. of triethylene melamine per week is now in progress.

In patient No. 2 (Table 1), because of active pulmonary tuberculosis, no ACTH or cortisone therapy has been administered. In this patient 3 excellent remissions have been observed following nitrogen mustard therapy. Repeated chest films and sputum studies have failed to show exacerbation of her pulmonary tuberculosis during or following the course of her therapy.

In only one patient (patient No. 5, Table 1) controlled by ACTH were we unable to obtain any remission with nitrogen mustard, although responses to ACTH have been excellent and prolonged.

When a response to nitrogen mustard or triethylene melamine is obtained all symptomatology is controlled. Skin eruptions disappear (Fig. 1), fever, pain and arthropathies are promptly controlled, and in patient No. 2 (Table 1) there was rapid control of severe secondary hemolytic anemia and epileptiform seizures. In those patients benefiting from nitro-

gen mustard therapy there is a definite decrease in the number of "L.E." cells in the bone marrow.

Both nitrogen mustard and triethylene melamine have a deleterious effect upon hematopoiesis. As many patients with acute disseminated lupus erythematosus have marrow damage as a result of their disease the possibility of a fatal, therapeutically induced agranulocytosis is more than a theoretical problem. For this reason, considerable caution must be exercised in administering these agents. It has been our practice to initiate therapy with a nitrogen mustard dose of 0.1 mg./kg. body weight. We have then allowed 2 to 4 days to elapse before repeating this dose, following the patient with repeated daily complete counts which includes quantitation of reticulocytes and circulating blood platelets. In no patient have we exceeded a total dosage of 0.4 mg./kg. body weight of nitrogen mustard in a therapeutic course. Improvement in our experience is observed promptly, starting 24 to 48 hours after the initial dose.

In only one of these patients (patient No. 1, Table 1) have we given corticosteroid therapy and nitrogen mustard concomitantly. We have not attempted maintenance therapy with either nitrogen mustard or triethylene melamine because of the troublesome marrow hypoplasia which follows prolonged therapy with these agents. Our experience with patient No. 1 (Table 1) would suggest, however, that maintenance therapy with triethylene melamine, particularly, is feasible if combined with maintenance corticosteroids to protect the marrow. It would seem that the amount of these agents could be reduced when used in such combination.

Mode of Action of Nitrogen Mustard and Triethylene Melamine. Some investigators feel that nitrogen mustard and triethylene melamine are effective because of their stimulation of the pituitary-adrenal axis[15,17]. Schlang[16], however, observed that, though both nitrogen mustard and corticosteroids were effective in suppressing the Schwartzman phenomenon when injected bacterial filtrate was employed, only nitrogen mustard was capable of suppressing this reaction provoked by antigen-antibody *in vivo* in rabbits.

It is our impression in this small series that nitrogen mustard and triethylene melamine are not effective solely on the basis of their stimulation of pituitary or adrenal glands. We base this impression on several observations. It can be seen in Fig. 2 that whereas nitrogen mustard caused no change in, or a slight increase in the gamma globulin curve on electrophoresis, ACTH in both patients in whom it was employed caused a significant fall in the gamma globulin percentage.

Furthermore, it can be seen in patient G.K. (Table 2) there was a significant rise in 17-ketosteroid and 11-oxysteroid excretion following ACTH therapy, although in neither patient G. K. nor B. S. (Table 2) did a significant elevation in these values follow nitrogen mustard or triethylene melamine therapy.

It has been previously noted that when patient No. 1 (Table 1) became refractory to ACTH, addition of nitrogen mustard effected a remission. It would not seem probable that 0.1 mg./kg. body weight of nitrogen mustard would further stimulate an adrenal cortex that was refractory to a daily dose of 60 mg. of ACTH. It should also be noted that patient No. 5 (Table 1) was responsive to moderate dosage of ACTH yet his symptomatology was completely refractory to 0.4 mg./kg. body weight of nitrogen mustard even though use of this agent resulted in

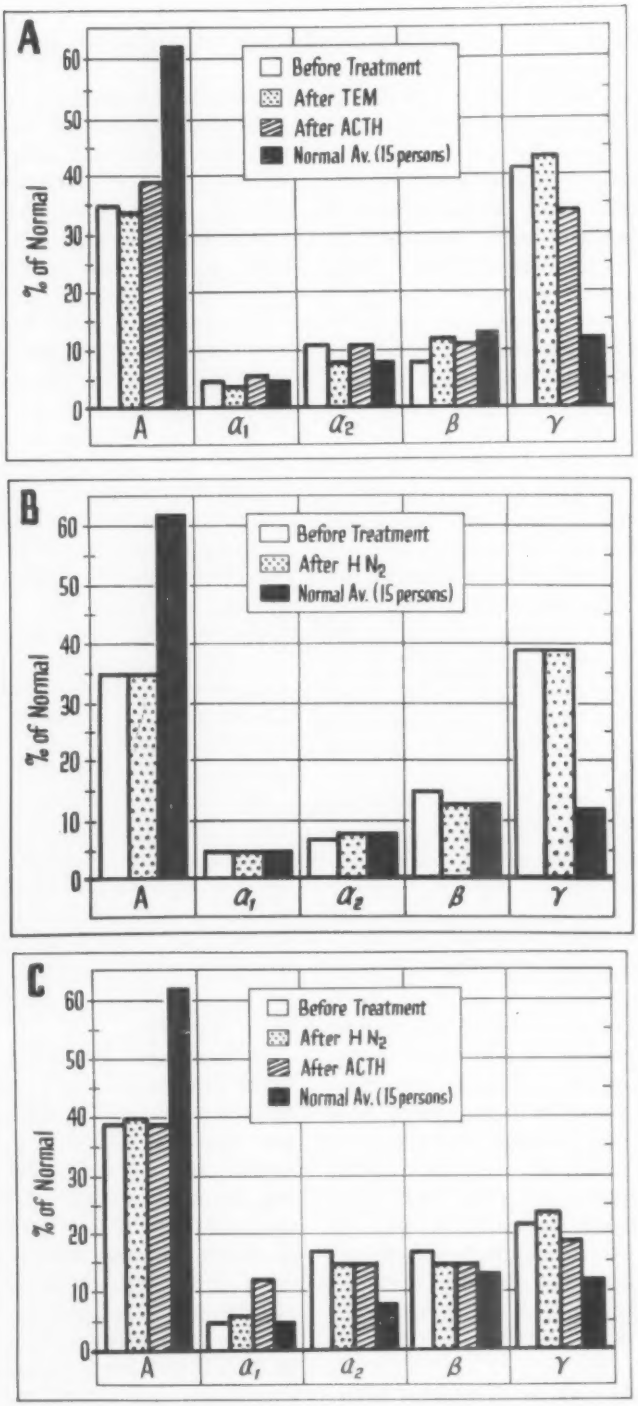


Fig. 2.– Electrophoretic analyses of sera from 3 patients before therapy and after therapy with nitrogen mustard (HN_2), triethylene melamine (TEM), and ACTH. Analysis at pH 8.6 in 0.1 M. veronal buffer. (A) Patient No. 1 (Table 1). (B) Patient No. 2 (Table 1). (C) Patient No. 5 (Table 1).

some elevation of his 17-ketosteroid and 11-oxysteroid excretion levels.

INDICATIONS FOR USE OF NITROGEN MUSTARD IN ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS. It is our impression that nitrogen mustard has some therapeutic benefit in acute disseminated lupus erythematosus; although, good results do not seem to be as consistent or as prolonged as those seen following ACTH and cortisone therapy.

In those patients in whom complicating infections, psychoses, intolerance of, or refractoriness to, corticosteroids interdicts the employment of these drugs, a trial of nitrogen mustard therapy would seem to be indicated.

Dubois[5] describes an acute crisis of lupus erythematosus which requires massive corticosteroid therapy. When nitrogen mustard proved effective in our patients, beneficial results were obtained quite rapidly and, in patient I.B. (Table 3) what had the appearance of an acute crisis responded very promptly to nitrogen mustard therapy. It is our opinion that nitrogen mustard might be indicated in such critical situations alone or in combination with corticosteroids.

Haserick and Corcoran[8] have found that nitrogen mustard therapy was beneficial in those patients with considerable renal involvement. We have had no personal experience with this complication and can only cite their experiences.

It would seem of some theoretical value to combine nitrogen mustard and corticosteroid therapy. Our experience would suggest that these agents might prove to be synergistic in some patients. If such should be the case lower dosage of both drugs might diminish the toxic effects of these agents and maintain patients in better remission for longer periods.

Summary. 1. We have employed nitrogen mustard and triethylene melamine therapy in 5 patients in whom we could obtain satisfactory follow-up studies.

2. Of these 5 patients, 3 showed remissions which varied in duration from 6 to 217 days.

3. The results are contrasted with those obtained in 4 of these 5 patients who also received corticosteroid therapy.

4. It is our impression that the effects of nitrogen mustard and triethylene melamine are not mediated solely through adrenal cortical stimulation, although we were unable to determine how these agents were effective.

5. Mode of administration was discussed and the hazards of employing such cytolytic agents in this disease process was noted.

6. It is our impression that nitrogen mustard and triethylene melamine are useful drugs in the treatment of acute disseminated lupus erythematosus, and indications for such therapy are suggested.

ACKNOWLEDGMENTS: We are indebted to S. M. Swingel, Ph.D., of Eli Lilly Research Laboratory, Indianapolis, Indiana for electrophoretic studies and to R. L. Dryer, Ph.D., Special Clinical Biochemist, Indiana University Medical Center, Indianapolis, Indiana, for steroid excretion studies.

REFERENCES

1. Cazenave, A.: Ann. des mal. de la peau et de la Syph., **3**, 297, 1851.
2. **Chasis, H., Goldring, W.,** and **Baldwin, D. S.:** Proc. Soc. Exper. Biol. & Med., **71**, 565, 1949.
3. **Diaz, C. J.:** Ann. Rheumat. Dis., **10**, 144, 1951.

4. **Diaz, C. J., Garcia, E. L., Merchantee, A.,** and **Perianes, J.**: J. Am. Med. Assn., **147**, 1418, 1951.
5. **Dubois E. L.**: Med. Clin. North America, **36**, 1111, 1952.
6. **Dubois, E. L., Commons, R. R., Starr, P., Stein, C. S.,** and **Morrison, R.**: J. Am. Med. Assn., **149**, 995, 1952.
7. **Fox, R. A.**: Arch. Path., **36**, 311, 1943.
8. **Haserick, J. R.,** and **Corcoran, A. C.**: Personal communication.
9. **Hebra, F.,** and **Elfinger, A.**: Atlas der Hautkrankheiten, Baumüller, Wien, **1856**.
10. **Kaposi, M. K.**: Arch. Dermat. u. Syph. **4**, 36, 1872.
11. **Klemperer, P., Pollack, A. D.,** and **Baehr, G.**: J. Am. Med. Assn., **119**, 331, 1942.
12. **Plaza de los Reyes, M.,** and **Monsalve y Americo Antillo, J.**: Rev. Med. Chile, **80**, 176, 1952.
13. **Roda, E.**: Am. J. Ophth., **35**, 114, 1952.
14. **Taylor, R. D., Corcoran, A. C.,** and **Page, I. H.**: J. Lab. & Clin. Med., **36**, 996, 1950.
15. **Salomon, M. I.**: New York J. Med., **52**, 1310, 1952.
16. **Schlang, H. A.**: Proc. Soc. Exper. Biol. & Med., **79**, 639, 1952.
17. **Shutkin, N. M.**: J. Bone & Joint Surg., **33A**, 265, 1951.
18. **Soffer, L. J.,** and **Bader, R.**: J. Am. Med. Assn., **149**, 1002, 1952.
19. **Waldbott, G. L.**: Ann. Allergy, **10**, 428, 1952.

PRESERVATION OF PLATELETS*

By James L. Tullis, M.D.

ASSOCIATE DIRECTOR OF THE BLOOD CHARACTERIZATION AND PRESERVATION LABORATORY, HARVARD UNIVERSITY; SPECIAL ASSOCIATE IN CYTOLOGY TO UNIVERSITY LABORATORY OF PHYSICAL CHEMISTRY RELATED TO MEDICINE AND PUBLIC HEALTH, HARVARD UNIVERSITY, BOSTON, MASSACHUSETTS

Platelets recently have become available for preservation and study, largely as a result of the application of knowledge concerning non-wettable surfaces and the development of techniques for Formed Element Separation[17]. The importance of non-wettable surfaces was appreciated by the Italians as long as 50 years ago; wherein direct transfusions using paraffin-coated syringes were used to reverse the bleeding tendency in thrombocytopenic purpura. With the development of citrate as an anticoagulant by Lewisohn in 1915[10], however, it became possible to store "blood" in glass bottles for later indirect transfusion, and the importance of non-wettable surfaces often was overlooked thereafter. Leukocytes and platelets were no longer present in significant numbers and the transfusion of blood became largely the transfusion of red cells and partially denatured plasma. Due to the known paucity of platelets in stored blood, it became generally assumed that these elements were fragile. As recently as 1949[13], there was general agreement that platelets could not be sustained outside the body more than 3 days. Present work shows, to the contrary, that platelets are hardy cells. With proper attention to surfaces and environment, these cells can be preserved for a period of time far in excess of either red cells or white cells.

Methods. The platelets used in these experiments were separated from fresh donor blood which had passed over non-wettable surfaces. Anticoagulation was effected by passage of the blood over a cation exchange resin column or by collection into plastic bags containing standard anticoagulant acid citrate dextrose (ACD) solution. Subsequent isolation was effected by any of 3 methods: 1) elution of the platelets which had complexed with the resin beads[7]; 2) concentration of the platelets which had not complexed with resin beads by passage of resin plasma through a specially designed falling-film centrifuge; 3) concentration of platelets from ACD plasma after a preliminary spontaneous red cell sedimentation. Gravity flow was employed throughout with avoidance of foaming or unnecessary agitation. Blood was chilled by passage through a heat exchange column. A temperature of 4° C. was attained promptly after leaving the antecubital vein and was maintained subsequently at this level throughout the period of preservation.

Platelets were found to survive in many different types of media. As noted by Alexander and Goldstein[1], a simple saline solution was sufficient to give fairly normal morphology for 1 to 2 weeks. In general, however, platelets retained better morphology in a protein-containing media and one which was hypertonic with respect to crystalloids. As in the case of leukocytes, gelatin proved singularly satisfactory as a colloid. Its optimal concentration varied between 1.5% and 2%. It was felt that the supportive effect of gelatin was largely due to its physical properties rather than its amino acid components. At the storage temperature of 4° C., it behaved as a solid mold which rapidly reverted

*This work has been supported by funds of Harvard University and the Eugene Higgins Trust, by grants from the Rockefeller Foundation, The Atomic Energy Commission, The National Institutes of Health, and by contributions from industry.

This is Number 4 in the series on "The Separation, Characterization and Preservation of the Formed Elements of the Blood," and it is also Number 106 in the series on "The Preparation and Properties of Serum and Plasma Proteins."

to a non-viscid liquid on rewarming to body temperatures. It was found that the crystalloids need not be complex. No buffering agent was necessary.

Sodium acetate, the only crystalloid other than sodium chloride and glucose, was added to the preservation media in a final concentration of 0.2 gm. per 100 cc. for its empiric effect against nonspecific cellular clumping. Forty cubic centimeters of final solution was used for the platelets derived from 500 cc. of blood. The composition of the media was as follows: Glucose 5.0 gm. per 100 cc., sodium chloride 0.85 gm. per 100 cc., sodium acetate 0.2 gm. per 100 cc., sterile gelatin* solution 2.0 gm. per 100 cc. Glucose was used primarily for tonicity effect rather than nutrition.

Results. The "viability" of a platelet can be assayed only by 1) retention of morphology, 2) retention of physiologic activity (clot promoting ability and/or clot retraction), and 3) ability to survive on reinfusion into platelet deficient recipients.

1) Retention of Morphologic Integrity. Significant numbers of platelets have now been preserved for up to one year (Table 1). By the end of this time, considerable morphologic change has occurred often giving the platelets a faded, empty appearance yet measurable clotting effects have persisted. The changes in morphology progress slowly throughout storage and the significance of the various forms has not yet been delineated. In the beginning, the majority of the platelets have a characteristic fibrillar appearance. When viewed under phase microscopy as a fresh specimen, they appear as brilliant blue cells with a homogeneous intracellular matrix and many tenuous filaments. In Fig. 1, fibrils may be seen radiating outward from 2 platelets photographed by electron microscopy. It is manifest that cells with such a network of surface fibrils would tend to adhere to rough surfaces. As storage proceeds, the platelets slowly lose these filaments and assume the more familiar symmetrical shape seen in ordinary stained preparations. There is sometimes a formation of a broad membrane around the platelets but these latter changes resemble the degenerative rupture seen when a fresh platelet spreads out on a foreign surface. The short, blunt spicules which emerge from this membranous material resemble the surface processes described by Fonio[6], Bessis[3] and others, but appear decidedly different from the type of fibrillar network noted in Fig. 1.

The total number of normal appearing platelets, both with and without surface fibrils, gradually decreases during storage. There is a concurrent increase in numbers of blebbed and ballooned forms as cellular deterioration continues. The method used in the original platelet isolation, prior to preservation, has significant effect on the speed with which these degenerative forms appear (Table 2). Normal morphology is exhibited longest in platelets originally collected into plastic bags containing ACD solution. Normal morphology is exhibited next longest in platelets isolated from plasma which has been decalcified by passage over a cation exchange resin (Dowex) column. Normal morphology is exhibited shortest in platelets which are isolated by interaction with resin beads followed by subsequent elution. In all instances the platelets were concentrated and separated from their plasma or their resin elution fluid by passage through a plastic, falling-film centrifuge bowl followed by resuspension in standard platelet preservation media.

2) Retention of Physiologic Activity. *Clot Promoting Ability:* No apparent correlation exists between the

*Sterile, aqueous, pyrogen-free P-10 gelatin solution (8.5%) specially prepared for this project by Dr. D. Tourtellotte of the Knox Gelatin Company.

TABLE 1.—PRESERVED PLATELETS

VARIATION IN PLATELET COUNT DURING STORAGE*

Time of Preservation (months)

Specimen	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
P-51-A	108,000	120,000	140,000	—	106,000	—	99,000	—	82,000				
P-51-R	32,000	28,000	20,000	—	26,000	—	—	14,000					
P-50-A	340,000	240,000	—	250,000	242,000								
P-40	65,000	—	—	—		—	74,000	—	—	48,000	30,000	—	30,000
P-52-A	340,000	340,000	236,000	—	212,000		225,000	205,000	—	168,000			
A-00231-N	366,000	—	202,000	—	—	—	176,000						
A-00234-N	356,000	—	—	—	—	—	162,000						
A-00249-N	302,000	—	—	—	234,000								
A-00365-N	122,000	—	—	—	68,000								
A-00418-N	302,000	—	172,000										

* Due to difficulty in securing exactly uniform distribution of platelets throughout the media during gelling, a significant error in total platelet count exists.

TABLE 2.—PRESERVED PLATELETS

EFFECT OF DIFFERENT MEANS OF COLLECTION ON VARIATION OF MORPHOLOGIC FORM DURING STORAGE

	Time of Preservation (months)					
Type Collection	*0*	*1*	*2*	*4*	*6*	*7*
ACD						
*Morphologic Form**	*Feb. 25*	*March 25*	*April 24*	*June 20*	*August 3*	*Sept. 26*
Normal with Fibrils	62	40	20	18	12	16
Normal without Fibrils	28 (90)	33 (73)	43 (63)	40 (58)	46 (58)	26 (42)
Blebbed	10	23	35	36	31	28
Ballooned	0	4	2	6	11	30
RESIN BLOOD (DOWEX)						
PLATELETS NOT COMPLEXED ON RESIN BEADS						
Normal with Fibrils	46	22	16	18	11	—
Normal without Fibrils	22 (68)	31 (53)	40 (56)	38 (56)	41 (52)	—
Blebbed	30	29	36	28	26	—
Ballooned	2	18	8	16	22	—
RESIN BLOOD (DOWEX)						
PLATELETS COMPLEXED ON RESIN BEADS AND SUBSEQUENTLY ELUTED						
Normal with Fibrils	44	34	21	12	8	—
Normal without Fibrils	22 (66)	20 (54)	24 (45)	30 (42)	16 (24)	—
Blebbed	26	34	31	26	31	—
Ballooned	8	12	24	32	45	—

* Morphologic Classification devised by G. Kemp

morphology of preserved platelets and their functional behavior. It was found that thromboplastic activity was retained even after specimens showed a high proportion of blebbed, ballooned and deteriorated forms. Although a gradual loss of clot promoting ability occurred, even the most damaged specimens were able to shorten the recalcification time of platelet-free plasma. It was believed that recalcification time did not represent a critical test of thromboplastic activity, however, due to the possible variability of many accelerator factors in the fresh plasma used in the test. The bulk of studies on preserved platelets, therefore, was carried out in a two-stage prothrombin conversion system. The platelets were assayed in a standard incubation mixture for accellerator activity alone (by substitution for Ac Globulin); for thromboplastic activity alone (by substitution for rabbit brain thromboplastin) and for both activities together (Fig. 2). It was found that the platelets alone, without the addition either of rabbit brain thromboplastin or beef serum Ac Globulin would convert prothrombin to thrombin. In Fig. 3, a series of successive curves shows the gradual loss of such activity in preserved platelets.

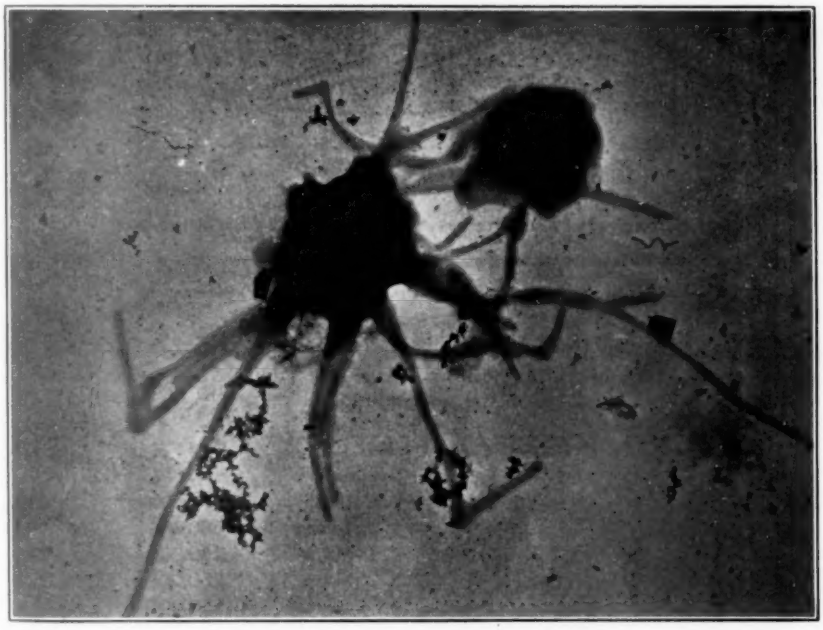


Fig. 1.—Two Platelets Showing Characteristic Fibrils—Magnification x 16800. (Electron Microscopy by courtesy Dr. Jerome Gross and Mrs. Zelda Sokol.)

In this experiment the curves were derived with a standard incubation mixture consisting of prothrombin, preserved platelets, imidazole buffer and acacia.

When platelets are removed from their preservation media, the rate of subsequent deterioration of morphology and thromboplastic activity resembles that which obtains at the time of original preservation. In the

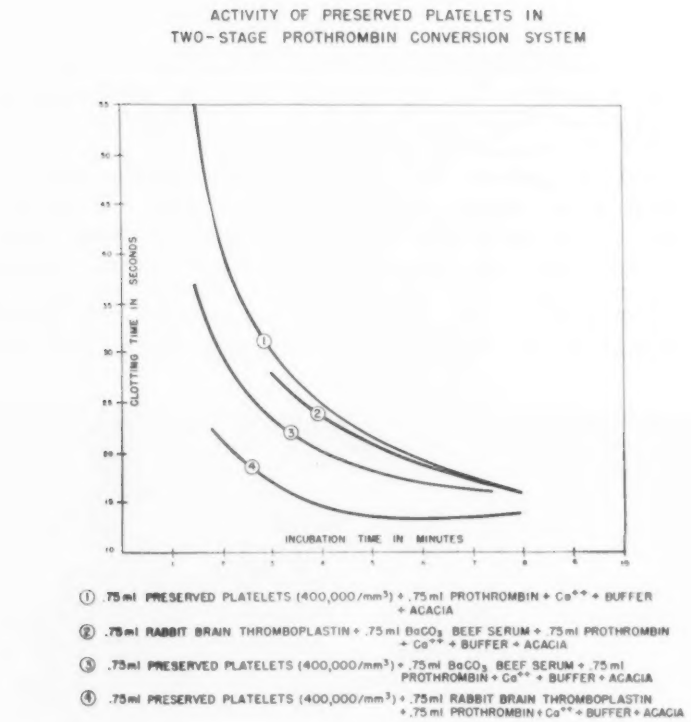

ACTIVITY OF PRESERVED PLATELETS IN
TWO-STAGE PROTHROMBIN CONVERSION SYSTEM
CLOTTING TIME IN SECONDS
INCUBATION TIME IN MINUTES
① .75ml PRESERVED PLATELETS (400,000/mm³) + .75ml PROTHROMBIN + Ca++ + BUFFER + ACACIA
② .75ml RABBIT BRAIN THROMBOPLASTIN + .75ml BaCO3 BEEF SERUM + .75ml PROTHROMBIN + Ca++ + BUFFER + ACACIA
③ .75ml PRESERVED PLATELETS (400,000/mm³) + .75ml BaCO3 BEEF SERUM + .75ml PROTHROMBIN + Ca++ + BUFFER + ACACIA
④ .75ml PRESERVED PLATELETS (400,000/mm³) + .75ml RABBIT BRAIN THROMBOPLASTIN + .75ml PROTHROMBIN + Ca++ + BUFFER + ACACIA

Fig. 2.— Activity of Preserved Platelets in Two-Stage Prothrombin Conversion System. Points obtained by clotting time of 1% fibrinogen solution after addition of 0.4 cc. of incubation mixtures as indicated.

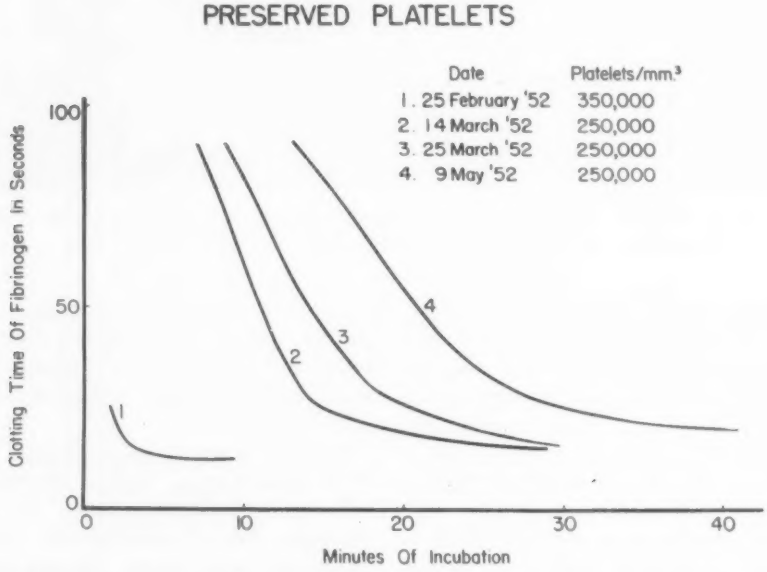


Fig. 3.— Decrease in Thromboplastic Activity of Platelets during Preservation. Points obtained by clotting time of 1% fibrinogen solution after addition of 0.4 cc. aliquots following incubation mixture: 0.75 cc. prothrombin eluate; 0.75 cc. platelets suspension; 0.25 cc. imidazole buffer pH 7.32; 0.25 cc. 1.0% $CaCl_2$; 0.25 cc. acacia; 0.75 cc. saline 0.85%.

experiment recorded in Fig. 4, a specimen of platelets which had been preserved 10 weeks, was ungelled, washed 3 times in saline-acetate and then allowed to stand in the wash solution at 4° C. for 6 days. At the end of this time the platelets, although less active than a standard rabbit thromboplastin mixture, still showed favorable ability to convert prothrombin. An aliquot which had stood for 8 days showed decidedly less activity. An aliquot which had stood for 10 days was still less active. Thus, although prothrombin conversion activity was retained for 10 weeks in the preserved gelatin mold, a significant drop in activity occurred over a few days period following removal from the preservation media and resuspension in a saline wash.

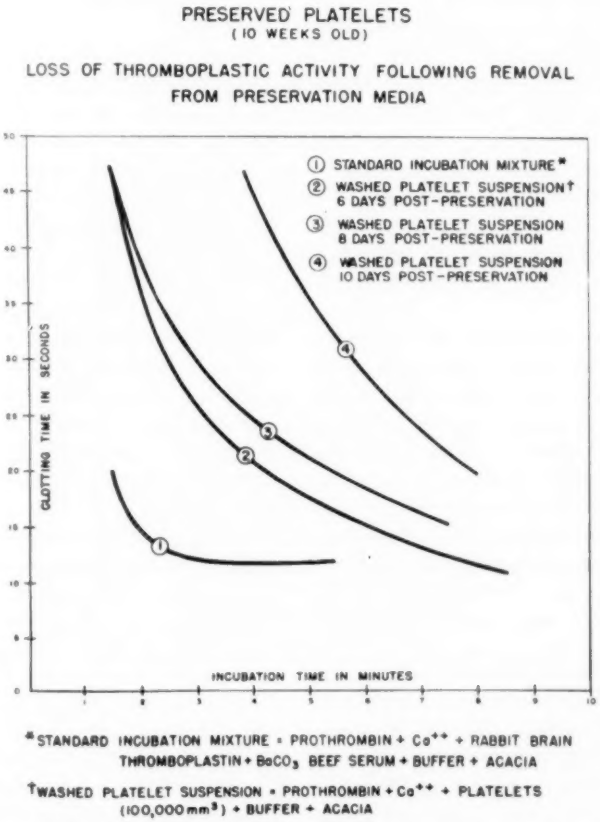

PRESERVED PLATELETS
(10 WEEKS OLD)
LOSS OF THROMBOPLASTIC ACTIVITY FOLLOWING REMOVAL FROM PRESERVATION MEDIA
① STANDARD INCUBATION MIXTURE*
② WASHED PLATELET SUSPENSION† 6 DAYS POST-PRESERVATION
③ WASHED PLATELET SUSPENSION 8 DAYS POST-PRESERVATION
④ WASHED PLATELET SUSPENSION 10 DAYS POST-PRESERVATION
CLOTTING TIME IN SECONDS
INCUBATION TIME IN MINUTES
*STANDARD INCUBATION MIXTURE = PROTHROMBIN + Ca++ + RABBIT BRAIN THROMBOPLASTIN + BaCO3 BEEF SERUM + BUFFER + ACACIA
†WASHED PLATELET SUSPENSION = PROTHROMBIN + Ca++ + PLATELETS (100,000 mm3) + BUFFER + ACACIA

Fig. 4.—Decrease in Thromboplastic Activity of Platelets after Removal from Preservation Media. Points obtained by clotting time of 1% fibrinogen solution after addition of 0.4 cc. of incubated mixtures as indicated.

Clot Retraction: Due to the large amounts of material necessary for study of clot retraction and due to the unexpected length of preservation that developed while this work was in progress, little study of retraction was undertaken. In a few instances where

tested, however, a rapid loss of clot retraction ability was noted. The possible relation of loss of this function to decrease in the number and size of platelet fibrils is discussed elsewhere[14].

3) TRANSFUSION OF PRESERVED PLATELETS. Transfusion of platelet-rich blood obtained from polycythemic donors has been employed by Hirsch[8] and others in the treatment of bleeding phenomena associated with deficiency of blood platelets. Such transfusions have usually met with success. The occasional instances, where little or no rise in circulating platelets could be demonstrated, were secondary to recipient factors, rather than any difficulty with the technique of collection or reinfusion of the polycythemic blood.

The platelets preserved by the techniques outlined above were selectively transfused into individuals in whom no anti-platelet factors could be demonstrated *in vitro*[16]. Recipients No. 1 and No. 2 had aleukemic leukemia with deficient megakaryocyte production and thrombocytopenia. Recipient No. 3 had pancytopenia, secondary to drug idiosyncrasy. Twenty-one platelet transfusions were administered to these 3 recipients.

The platelets were preserved by the methods outlined above. They were isolated from whole blood by complexing onto Dowex resin beads with subsequent saline elution in the first 3 transfusions. In the other 18 transfusions, the platelets were isolated from plasma by differential centrifugation after a preliminary red cell sedimentation. Approximately 20 minutes was allowed for infusion of the material. Special care was taken to maintain non-wettable surfaces throughout all equipment. Platelets were given within blood type, although no evidence of ABO grouping in platelets has been noted in this laboratory.

The platelets were not removed from the gelatin preservation media at the time of transfusion. The media, consisting of a 40 cc. gel was liquefied by warming the plastic storage bag to body temperature. It was then added to a small volume of intravenous saline solution.

Recipient No. 1. (CG) received 2 platelet transfusions approximately 2 weeks apart. At the time of administration of preserved platelets, the peripheral platelet count was 28,000 per c. mm. Fig. 5 shows the subsequent fate of the infused platelets. There was a rise in count to 42,000 per c.mm. with a return to the previous platelet level after a 3-day period. Although the total rise in platelet count was of small increment, it was believed significant*. Coincident with this slight rise in count, there was a prompt cessation of hemorrhagic phenomenon and a return in capillary bleeding time to normal levels. The degree of clinical improvement seemed out of proportion to the number of platelets administered. The patient remained free of further bleeding tendencies for a period of 10 days. The second platelet infusion was given 14 days later. The fate of the transfused platelets was essentially similar to the first instance. There was again a clinical improvement manifest by cessation of all bleeding tendencies. The platelets administered to this individual had been preserved one day in the first instance and one week in the second instance. The patient expired of her underlying leukemic process 4 weeks after the second platelet infusion.

Recipient No. 2. (FS) received 2 units of preserved platelets. At the time of the first platelet transfusion,

*All counts were done as divided specimens by the method of Brecher and Cronkite under phase microscopy. The statistical accuracy of this method previously has been determined[4].

acute leukemia had been present 4 months. Clinical evidence of purpura had been present for 2 days. The platelet count had been depressed throughout the entire 4-month period. The first platelet transfusion consisted of all of the platelets derived from 2 units of blood. Following the first platelet infusion, there was a rise in circulating numbers of platelets from 22,000 to 40,000 per c. mm. with a subsequent fall after 48 hours to a level slightly below the original level. Bleeding tendencies stopped shortly after the infusion, but recommenced the following day. A second platelet infusion with platelets from one unit of blood resulted in a slight rise (35% increase in total count) with a return to preinfusion level the following day. The preserved platelets given to this individual had been preserved for 2 and 3 weeks respectively. Due to severe anemia, whole blood transfusions were subsequently given and no further data accumulated.

Recipient No. 3. (JMcA) (the only child in the series)* had pancytopenia which was believed to be secondary to drug sensitivity. During a 5-week period between the onset of illness and death from complete bone marrow exhaustion, 17 transfusions of preserved platelets were given as well as many blood transfusions. The patient was hospitalized in another city from that in which the platelets were prepared. The shipments were made by Air Express with the preserved platelets being maintained at 4° C. throughout. Due to the extremity of the patient's condition and the concurrent need for whole blood, accurate data could not be obtained with respect to fluctuation in count following platelet transfusions. In the few instances in which preserved platelets were given without concurrent blood, the patient's gen-

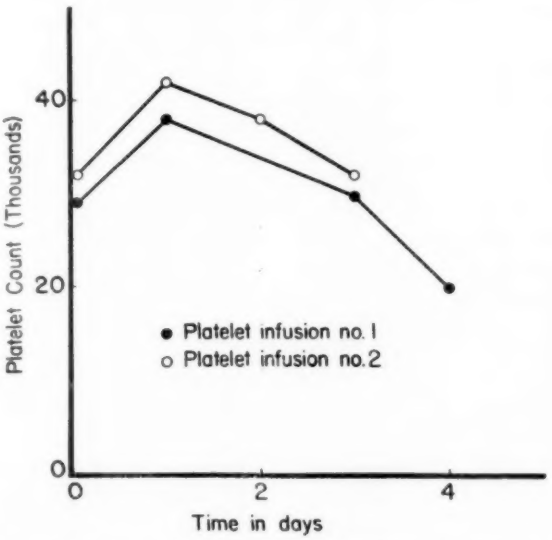


Fig. 5.—Fluctuation in Circulating Platelet Count Following Infusion of Preserved Platelets.

*Platelets administered by Dr. John Scudder to a patient under the care of Dr. Conrad M. Riley. Permission to reproduce their findings is gratefully acknowledged.

eral condition seemed little changed although note was made that there was a decrease in petechiae and bleeding phenomenon following some of the platelet infusions. The patient eventually became resistant to all forms of therapy and expired.

Discussion. The unexpected observation that the optimal media of platelet preservation need not contain a buffer, would seem to indicate that platelets have little or no metabolic activity, and indeed, evidence showing an absence of significant glucose utilization or lactic acid accumulation in preserved specimens bore this out[14]. Subsequent studies by Cartesian Diver Respirometry have showed only min-

TABLE 3.—PRESERVED PLATELETS

OXYGEN CONSUMPTION IN CARTESIAN DIVER

Diver 68		$K_{O_2} = 9.65 \times 10^{-4}$			
17	56	17	56	164.05	164.05
6	60	23	116	57.9	221.95
4	24	27	140	38.6	260.55
−1	29	26	169	9.65	270.20
		$\frac{1 \times 10^{-4}}{222{,}000 \times 1.5} = 0.3 \times 10^{-9}$			
Diver 57		$K_{O_2} = 9.77 \times 10^{-4}$			
9	58	9	58	87.93	87.93
5	55	14	113	48.85	136.78
2	25	16	138	19.54	156.32
0	26	16	164	0	156.32
		$\frac{0.85 \times 10^{-4}}{222{,}000 \times 1.5} = 0.26 \times 10^{-9}$			
Diver 60		$K_{O_2} = 9.59 \times 10^{-4}$			
−6.5	32	6.5	32	+62.335	62.33
−3.0	29	9.5	61	+28.77	91.10
−1.0	31	10.5	92	+9.59	100.69
−3.0	32	13.5	124	28.77	129.46
−2.5	34	16.0	158	23.92	153.39
−2.5	26	18.5	184	23.92	177.32
−0.0	29	18.5	213	0.0	177.32
−7.0	64	25.5	277	66.99	244.31
+2.0	51	23.5	328	19.14	225.17
		$\frac{0.633 \times 10^{-4}}{396{,}000 \times 1.5} = 0.11 \times 10^{-9}$			
Diver 69		$K_{O_2} = 7.8$			
−3	28	3	28	23.4	23.4
−4	26	7	54	31.2	54.6
−2.5	31	9.5	85	19.5	74.1
−1.5	31	11.0	116	11.7	85.8
−2.0	36	13.0	152	15.6	101.4
−2.0	25	15.0	177	15.6	117.0
−2.5	29	17.5	206	19.5	136.5
−2.5	67	20.0	273	19.5	156.0
+0.5	48	19.5	321	3.9	152.1
		$\frac{0.568 \times 10^{-4}}{396{,}000 \times 1.5} = 0.095 \times 10^{-9}$			

* Standard formula

$$\frac{\text{Slope of } \Sigma\Delta T/\Sigma\Delta V}{\text{Platelet count} \times \text{volume of plasma suspension}} = \text{oxygen consumption } (mm^3/\text{platelet/minute})$$

1. Apparatus furnished by Mr. Lloyd C. Claff, Marine Biological Laboratory, Woods Hole, Massachusetts
2. Data by Gareth Green and Shirley Kapsalis.

imal oxygen consumption in either freshly isolated or preserved platelets (Table 3). Moreover, Zamecnik and Baker[18] working with these same specimens were unable to demonstrate significant incorporation of C-14 labelled DL-leucine into intracellular platelet protein. Such findings are in distinct contrast to the rapid metabolic activity of preserved leukocytes, when studied by these same techniques[15]. The oxygen consumption in preserved platelets varied from 0.1 to 0.3 x 10^{-9}/mm^3/0_2/platelet/minute. This is about one 1/100 the respirometry rate of leukocytes studied under the same conditions.

The significance of the various morphologic forms observed during platelet storage has not been determined. It is of interest that platelets separated from ACD solution exhibited greater numbers of morphologically intact forms than platelets separated from blood collection over ion exchange columns. In the latter instance it should be noted, however, that the *rate* of morphologic degradation was no faster in preserved platelets that had been isolated from resin collections than ACD collections. This may represent a selective population of cells due to simple filtration of platelets having long filaments during the passage of venous blood through the resin bead. From a practical standpoint, it is of interest that clot promoting ability was not lost concurrent with degradation and morphology.

The ability of preserved platelets to convert prothrombin to thrombin in an isolated system was an unexpected finding. Unequivocal evidence has been brought forward previously by many workers to show that washed platelets alone possess little or no thromboplastic effect. It is generally accepted that formation of thromboplastin requires an interaction between platelets and some protein component of plasma. This concept of a plasma factor interacting with platelets to liberate thromboplastin was originally developed by Brinkhous[5] and Leggenhager[9], Quick[12], and Milstone[11]. More recently Alexander also has shown a definite "activation" of platelets by prior incubation with serum prothrombin conversion accelerator[2].

It must be assumed, therefore, that the unexpected ability of preserved platelets to convert prothrombin to thrombin in an isolated system was the result of an interaction between the platelets and the small amounts of plasma present on their surface during the period of preservation. Although the platelets always were washed 3 times after preservation and before testing in the two-stage prothrombin system, they were not similarly washed before preservation. The method of concentration in the falling-film centrifuge followed by elution and resuspension in the preservation media generally removed most of the plasma* but small amounts invariably were present.

This concept was supported by the observation that a triple wash of platelets before preservation markedly decreased their activity for prothrombin conversion in an isolated system free of plasma or serum accelerator factors.

A few salient facts were noted during the course of *in vivo* transfusions of preserved platelets: 1) Platelets could be reinfused into suitable thrombopenic recipients. 2) There was no apparent difference in the clinical effectiveness of platelets obtained from resin beads (3 cases) and those obtained by centrifuge methods (18 cases). 3) The survival time of trans-

*Estimates by dye dilution equals 0.4% plasma remaining in the final media.

fused platelets varied between 1 and 3 days. 4) The clinical effectiveness of transfused platelets was greater than would be expected from the slight rise in total count which followed their administration. 5) Platelets isolated and preserved by the techniques outlined above were free of pyrogens or toxic materials when reinfused into human recipients.

Summary. Methods for the preservation of platelets are delineated and discussed. Platelets appear relatively inert metabolically and can be preserved for periods of time far in excess of the other cellular elements of blood.

REFERENCES

1. **Alexander, B.**, and **Goldstein, R.**: Studies with Blood Clotting Components; Proceedings Second Harvard Conference on the Separation of the Formed Elements, the Protein, Carboyhdrate, Lipid, Steroid, Peptide and Other Components of Plasma, July 11, 1950, Boston, Mass.
2. **Alexander, B.**, and **Landwehr, G.**: Fed. Proceedings, **10**, 212, 1951.
3. **Bessis, M.**: Blood, **5**, 1083, 1950.
4. **Brecher, G.**, and **Cronkite, E. P.**: J. Applied Physiol., **3**, 365, 1950-51.
5. **Brinkhous, K. M.**: Am. J. Med. Sci., **198**, 509, 1939.
6. **Fonio, A.**, and **Schwendener, J.**: Die Thrombozyten des menschlichen Blutes, Verlat Hans Huber, Bern, 1942.
7. **Freeman, G.**: Science, **114**, 527, 1951.
8. **Hirsch, O., Favre-Gilly, J.**, and **Dameshek, W.**: Blood, **5**, 568, 1950.
9. **Leggenhager, K.**: Helv. Med. Acta, **1**, 527, 1935.
10. **Lewisohn, R.**: Surg., Gynec., & Obst., **21**, 37, 1915.
11. **Milstone, J. H.**: Proc. Soc. Exp. Biol. & Med., **68**, 224, 1948.
12. **Quick, A. J.**: Am. J. Med. Sci., **213**, 272, 1947.
13. **Tocantins, L. M.**: Preservation of Platelets; The Preservation of the Formed Elements and Proteins of Blood, American National Red Cross, Harvard Symposium, January 6-8, 1949, p. 70.
14. **Tullis, J. L.**: Blood Cells and Plasma Proteins, Academic Press, New York, 1953, p. 148.
15. Idem: Blood, in press.
16. Idem: Interaction of Platelets with Specific Plasma Proteins: Implications of New Knowledge About Amino Acids, Peptides, and Proteins, Enzymes, Antibodies and Viruses, Red Cells, White Cells and Platelets, and of the Fine Structure of Proteins for Protein Synthesis, Harvard Symposium, January 15, 1953.
17. Idem: Blood, **7**, 891, 1952.
18. **Zamecnik, P. C.**, and **Baker, W. H.**: Personal Communication.

THE USE OF ACTH IN PREPARING PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA FOR SPLENECTOMY*

By Richard W. Greene, M.D.
ASSISTANT PROFESSOR OF MEDICINE

William W. Faloon, M.D.
ASSISTANT PROFESSOR OF MEDICINE

AND

Eugene L. Lozner, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From the Department of Medicine, State University of New York at Syracuse, College of Medicine, Syracuse, New York.)

Although splenectomy has been the most widely recommended therapeutic measure in idiopathic thrombocytopenic purpura since Kaznelson[17] suggested it in 1916, it has not been uniformly successful nor able to be carried out without operative hazard. With the advent of ACTH and cortisone it has been demonstrated that these hormones are able to produce variable degrees of remission or symptomatic relief in thrombocytopenic states[20,35]. Most consistently, however, temporary reduction in capillary fragility and thus relief of hemorrhagic symptoms have resulted from such endocrine therapy[10]. By virtue of these effects it has been suggested that ACTH and cortisone could be used in the preparation of patients for splenectomy. In addition, it has been hoped that their use prior to surgery might reveal information concerning the predictability of the results of splenectomy. Accordingly, this study was undertaken in an attempt to evaluate the relationship of the effect of ACTH to prognosis after splenectomy, to ease of management before and during operation, and to postoperative wound healing.

The relationship of splenectomy to the "stress" reaction and humoral factors engendered by that reaction was suggested by Robson[30] who noted that the effect of this procedure could not be evaluated for several weeks after operation. Other workers have since reported experience with ACTH or cortisone and splenectomy in thrombocytopenic states with variable results. Meyers and her coworkers[20] reported a poor result with ACTH but with response to splenectomy in one patient. Bethel *et al.*[1], from the same clinic, later reported an expansion of their experience with these hormones in which 3 patients who were splenectomized showed quite diverse reactions. One of these, a 60-year old woman, had been splenectomized 5 months previous to giving ACTH without improvement. After ACTH and cortisone for nearly one month she had

* These studies were aided by a contract (NONR 12800) between the Office of Naval Research, Department of the Navy and Syracuse University, and by a contract (NONR 12801) between the Office of Naval Research, Department of the Navy and the State University of New York. Both of these contracts were supported jointly by the Office of Naval Research and the Atomic Energy Commission.

a rise in her platelet count and partial remission in her symptoms. Of the other two, a 3-year old boy transiently responded to cortisone both clinically and with a rise in platelets, then responded well to splenectomy; and a 15-year old girl obtained no response on ACTH and cortisone, then had a sustained clinical and hematological remission following splenectomy. This group also[21] reported another case of a 34-year old woman who had a good platelet rise initially with ACTH and also with cortisone but relapsed when the hormones were withdrawn. Subsequently while on cortisone she had splenectomy performed with a sustained remission for 9 months.

Wintrobe *et al.*[35] have recorded a moderate platelet response to ACTH followed by splenectomy and complete remission in one patient and Evans and Liu[9] have noted temporary hematologic and symptomatic relief while receiving ACTH in a patient who had relapsed following splenectomy. Jacobson and Sohier[16] have observed 3 patients demonstrating good responses to ACTH and cortisone of whom one was splenectomized. This resulted in a further platelet increase but only a 5-day follow-up was recorded. Fifteen patients were studied by Stefanini and his coworkers[31] with temporary remissions during hormonal therapy in most instances. Six underwent splenectomy, 3 before receiving such therapy. One was given ACTH 4 days postoperatively when bleeding became worse and a sustained remission was achieved. The second had a relapse a few weeks after splenectomy and ACTH then controlled the bleeding manifestations and was associated with a rise in platelets. The third had been splenectomized 3 years previously and then relapsed. Cortisone therapy yielded improvement in bleeding episodes and capillary fragility but no rise in platelets. The other 3 cases were given ACTH or cortisone prior to splenectomy. The first, a 5-year old girl, had a temporary rise of platelets and sustained improvement of capilliary fragility on ACTH. Two weeks after the hormone was stopped, splenectomy was performed with excellent therapeutic response. The second, a 6-year old girl, had a good platelet rise and disappearance of purpura on cortisone, then relapsed when it was stopped. A complete hematological and clinical remission was observed following splenectomy. The third, a 32-year old woman had no platelet rise but improved vascular fragility while receiving cortisone but splenectomy resulted in sustained clinical and hematological remission. Harrington *et al.*[14] studied 35 patients with idiopathic thrombocytopenic purpura. Eleven received ACTH or cortisone prior to splenectomy. Of these, one had a partial rise of platelets on cortisone, then had a remission after splenectomy. Five had no platelet rise on ACTH or cortisone, then had remissions after splenectomy and 5 had no response to these hormones preoperatively and no response to splenectomy. Three other patients had no response to splenectomy. Of these, 2 subsequently had no response to ACTH or cortisone. The other patient, who also had acquired hemolytic anemia, subsequently had a remission on cortisone.

Methods. Seven patients (6 females, 1 male) with "idiopathic" thrombocytopenic purpura, one of whom also had acquired hemolytic anemia, were studied. After suitable control periods, they were given ACTH or cortisone for periods deemed sufficient to note the response and were then splenectomized. All have been followed for periods varying from 2 months to 2 years after operation.

The ACTH administered to patients 2 and 7 was prepared by the National Drug Co. The rest of the ACTH used was prepared by the Wilson Laboratories. ACTX was pre-

pared by the National Drug Co. and was reported to be 4 times as active as ACTH.* ACTHAR gel was a long acting type of corticotropin prepared by the Armour Laboratories. The cortisone was manufactured by Merck & Co. The platelet and eosinophile counts were done by the method of Pohle and Pilot, respectively[24,25] and capillary fragility tests were carried out using a blood pressure cuff as described previously[12] with values above 15 petechiae per 2.5 cm. diameter area being considered abnormal. Clot retraction and prothrombin utilization were also measured but they correlated so closely with the platelet count that these results are not included.

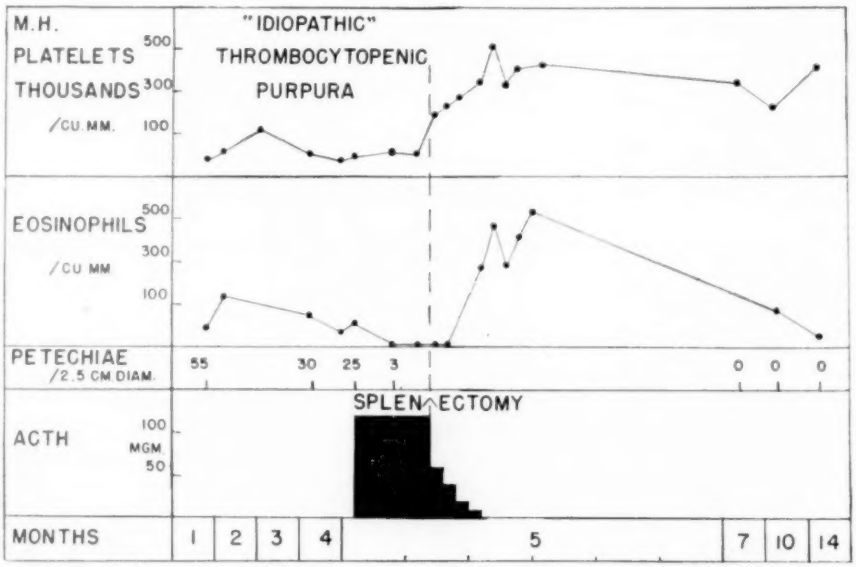


Fig. 1— No platelet response to ACTH but sustained remission after splenectomy in Patient 1. Note the variable time periods in abscissa to allow greater detail.

Results. CASE REPORTS‡†: *Patient 1:* M.H. (Fig. 1) was a 34-year old housewife who had a 3-month history of spontaneous bruising over the right leg and buttock and both arms. For one month she had noted occasional small purpuric spots. Also, one month before admission she had a mild attack of labyrinthitis. Physical examination was negative except for petechiae over her arms and legs. Blood studies were normal except for the low platelet count and sternal marrow aspiration showing increased numbers of megakaryocytes. On ACTH her vascular fragility decreased but the platelet count remained unchanged. Following splenectomy a rise in platelets occurred which has been sustained for 9 months with no purpuric symptoms.

This patient demonstrated no platelet response to ACTH but subse-

* The ACTX was kindly given to us by the National Drug Co.

† Patients 3 and 5 have previously been reported[10].

‡ Drs. George Reifenstein, Seymour Schwartzberg, Leon Goldstein, Helman Rubinson, Leon Berman and Norbert Reicher kindly referred patients No. 1, 2, 3, 4, 6, 7 respectively. The following surgeons performed the splenectomy on the indicated patients: Dr. Arthur Raffl, patient 1; Dr. Leon Berman, patients 2, 3 and 6; Dr. Daniel Burdick, patients 4 and 7; Dr. Richard Eberle, patient 5.

quently has had a sustained remission after splenectomy.

Patient 2: B.E. (Fig. 2) was a 27-year old married secretary who entered with a one-month history of spontaneous bruising. Except for a few ecchymoses of the legs she had no abnormal physical signs and the low platelet count was the only abnormality of the peripheral blood. Sternal marrow aspiration showed many eosinophils and megakaryocytes. On ACTH her vascular resistance improved and her platelets rose to 115,000 per c. mm., which was considered a significant increase. Following splenectomy the platelet count and tourniquet test remained normal for nearly 3 weeks. Two weeks post-operatively she had headache, weakness of right arm and leg which spontaneously cleared in one month. This was interpreted as a small cerebrovascular accident. At the time her platelet count was normal and the tourniquet test was negative. Approximately 5 weeks after splenectomy she had a return of easy bruising of the legs, the platelet count dropped to low values which have persisted for 9 months. Her purpuric manifestations are moderately severe but most distressing is menorrhagia which has been only partially controlled with oral cortisone.

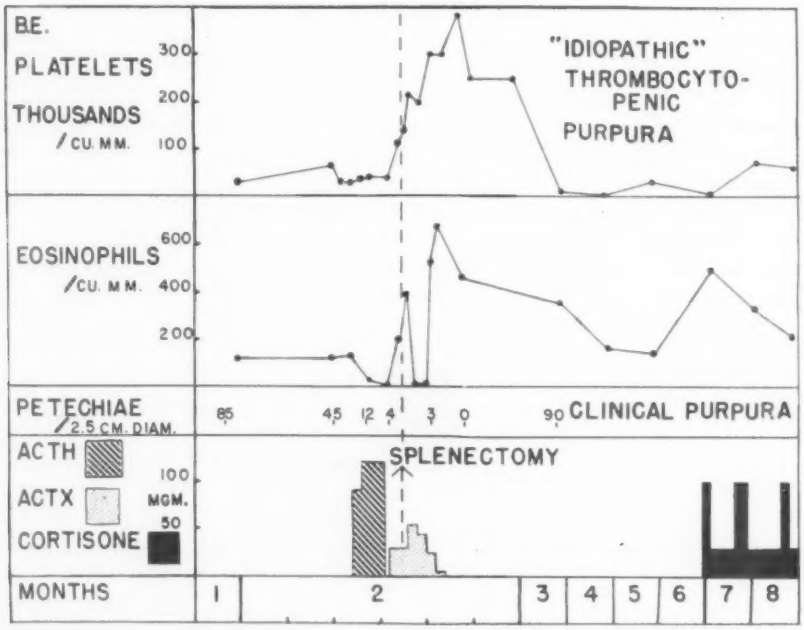


Fig. 2.— Moderate platelet response to ACTH but complete relapse after splenectomy in Patient 2. Note the variable time periods in abscissa to allow greater detail.

This patient had a moderate platelet rise with ACTH pre-operatively followed by complete relapse 5 weeks after splenectomy.

Patient 3: B.H. (Fig. 3) a 13-year old school girl, entered the hospital with a 3-month history of recurrent petechiae and ecchymoses of

the arms and legs. Physical examination was negative except for a few petechiae and blood studies were negative except for the low platelet count. Sternal marrow aspiration was within normal limits. While receiving 100 mg. of ACTH per day she had a remission of capillary fragility but no significant rise in her platelets. Improvement in both vascular fragility and platelet was reinstituted and splenectomy carried out. A good hematologic and clinical remission occurred and she has remained well for 17 months after operation.

This patient had a complete remission with ACTH followed by relapse when it was discontinued. Splenectomy was performed and she has main-

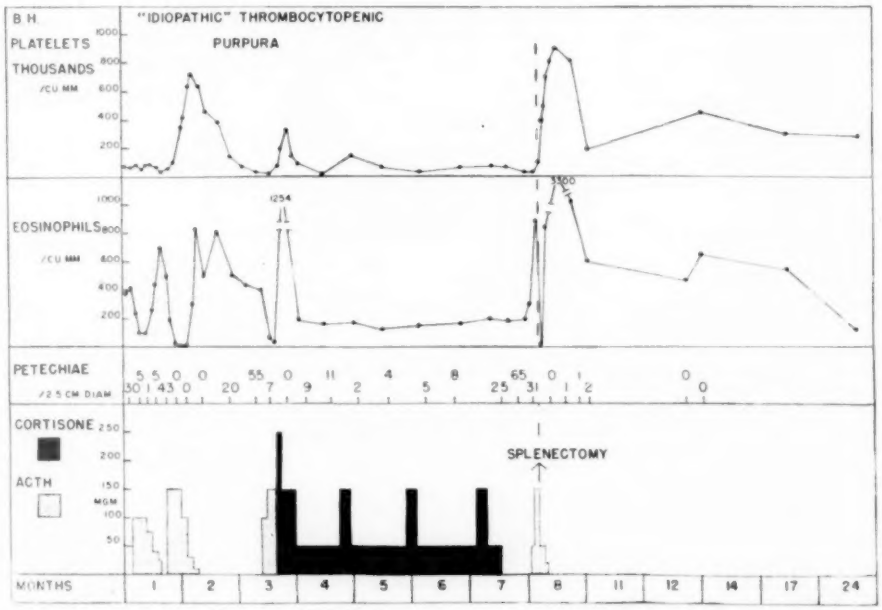


Fig. 3.— Excellent platelet response to ACTH and sustained remission after splenectomy in Patient 3. Note the variable time periods in abscissa to allow greater detail.

concentration occurred during a course of 150 mg. daily. With discontinuance of the ACTH she promptly relapsed. Seven weeks later, she again responded satisfactorily to ACTH and was subsequently for 4 months on 50 mg. daily of oral cortisone plus larger doses during her menstrual periods. During this interval her vascular fragility was normal although the platelet count remained low. Cortisone was then stopped for 2 weeks following which ACTH tained normal platelet counts and vascular fragility for 17 months.

Patient 4: M.B. (Fig. 4) was a 37-year old housewife who had easy bruising since childhood and severe menstrual bleeding. She had also had severe nose bleeds and excessive bleeding following a tooth extraction. Two weeks prior to admission she suddenly became unconscious and was hospitalized at another hospital. A lumbar puncture showed a subarachnoid hem-

orrhage and without specific therapy she improved slowly. A blood count there showed thrombocytopenia. Except for several subcutaneous ecchymoses and a hemorrhage in the left fundus, her physical examination was negative. The tourniquet test was borderline and blood studies were normal except for a hypochromic anemia and low platelet count. Sternal marrow aspiration showed moderate erythroid hyperplasia. ACTH therapy yielded no platelet response and following splenectomy she had only slight temporary improvement in her platelet count and her tourniquet test was not significantly changed. Her menorrhagia is slightly improved as is her bruising.

This represents a patient who had no platelet response to ACTH and only a slight transient increase in platelets following splenectomy.

Patient 5: J.K. (Fig. 5), a 49-year old male unemployed construction laborer, entered with a history of easy bruising of one month's duration. Physical examination was negative except for ecchymoses, acne, and mild hypertension. His blood was normal except for diminished platelets. Sternal marrow aspiration was consistent with idiopathic thrombocytopenic purpura and contained many eosinophils. On ACTH he had an increase in vascular resistance but no rise in platelets. Following splenectomy he had a return of platelets to normal levels which has been maintained for 15 months. No hemorrhagic symptoms have been noted except for a transient shower of petechiae 10 months post-splenectomy which spontaneously cleared.

This patient is one in whom preoperative use of ACTH produced no

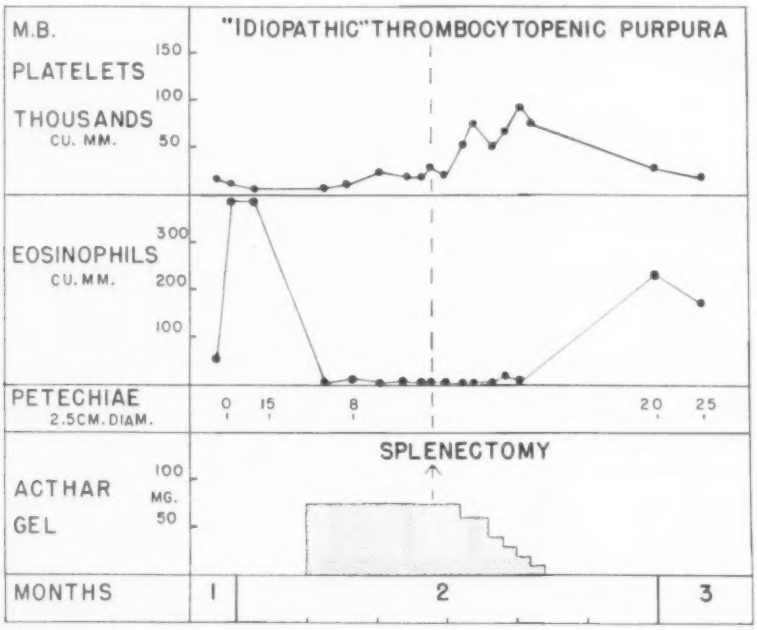


Fig. 4.— No platelet response to ACTH and relapse after splenectomy in Patient 4. Note the variable time periods in abscissa to allow greater detail.

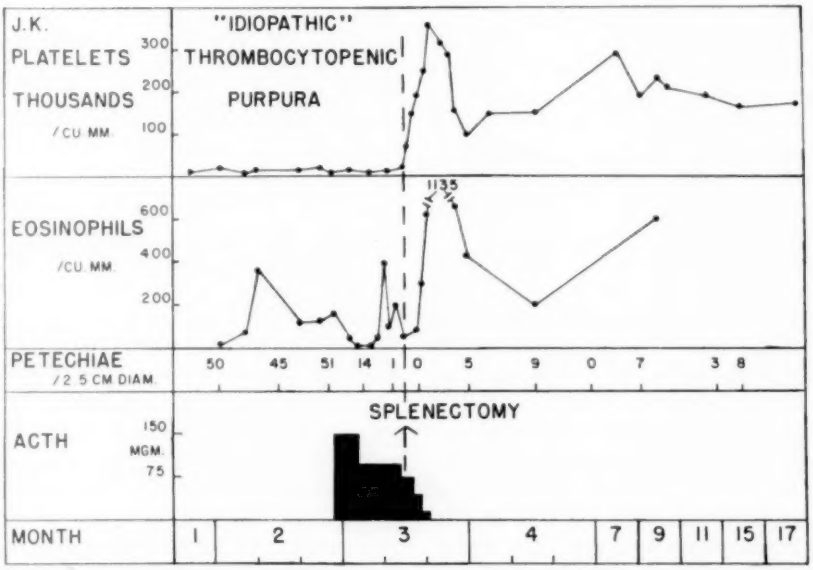


Fig. 5.— No platelet response to ACTH but sustained remission after splenectomy in Patient 5. Note the variable time periods in abscissa to allow greater detail.

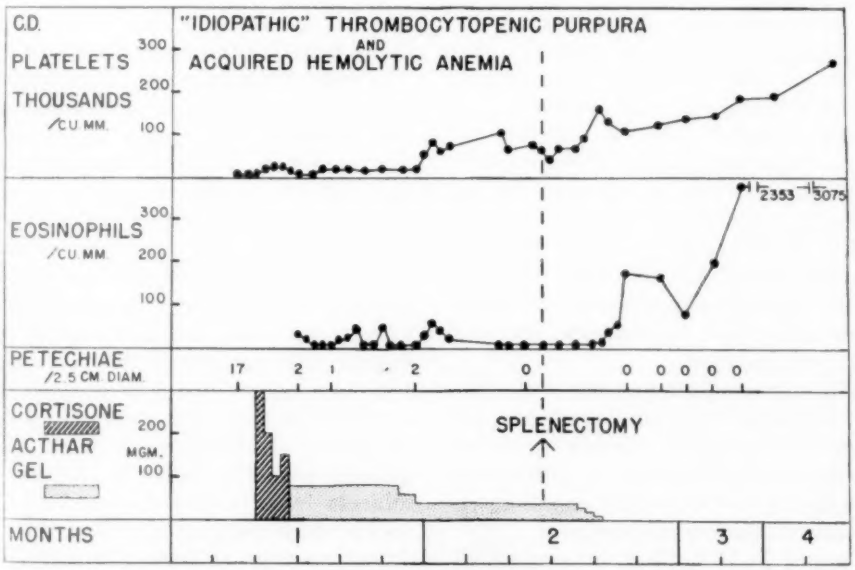


Fig. 6.— Partial platelet response to ACTH and complete remission after splenectomy in Patient 6. Note the variable time periods in abscissa to allow greater detail.

rise in platelets whereas splenectomy produced a permanent remission.

Patient 6: C.D. (Fig. 6), a 15-year old school girl, had a 6-months' history of easy bruising and a one-week history of dyspnea on exertion, dizziness and headache. Physical examination showed a pale, slightly icteric girl without petechiae. The tourniquet test was positive and hematologic studies showed an hematocrit of 18%; hemoglobin 6.3 gm.; red cell count 1.5 million per c. mm.; white cell count 6500 per c. mm.; with a normal differential; platelets 8000 per c. mm.; reticulocytes 12%; serum bilirubin 0.2 mg., direct, 1.7 mg. indirect. Direct and indirect Coombs' tests were negative. The osmotic fragility of freshly drawn blood was normal but after incubation for 24 hours the fragility curve was at the upper limits of normal.* The mechanical fragility of incubated red cells was above normal.* Presumptive tests for nocturnal and cold hemoglobinuria were negative. Sternal marrow aspiration showed erythroid hyperplasia but megakaryocytes were normal. The cause of the hemolytic anemia was never determined. On cortisone and ACTH normal vascular fragility returned but the platelet count rose insignificantly. After transfusions she underwent splenectomy with subsequent return of platelets and erythrocytes to normal levels and remains asymptomatic. Marked eosinophilia, the significance of which is unknown, occurred after splenectomy.

This represents a patient with idiopathic thrombocytopenic purpura and acquired hemolytic anemia who had a poor platelet response to ACTH preoperatively but who had complete remission following splenectomy.

Patient 7: H.Z. (Fig. 7) was a 26-year old housewife who had a one-year history of spontaneous bruising and menorrhagia of 4-years' duration. Except for numerous petechiae and ecchymoses over the trunk and extremities, the physical examination was negative. The tourniquet test was positive but peripheral blood studies were normal except for diminished platelets. Sternal marrow aspiration showed numerous normal appearing megakaryocytes and increased eosinophils. During ACTH therapy normal vascular fragility and a significant increase (to 200,000 per c. mm.) in the platelet count were observed. Six weeks postoperatively platelets fell to about 100,000 per c. mm. and have remained there and vascular fragility has become borderline. She continues to have bruising, though not as severe as pre-operatively and menorrhagia has decreased.

In this instance ACTH produced a good platelet response but splenectomy yielded an incomplete remission.

The results of this study are summarized in Table 1. For these 7 patients there was no operative mortality. The splenectomies were all performed without hemorrhagic complications and wound healing was unimpaired. No correlation between the preoperative platelet response to ACTH or cortisone and the result of splenectomy was observed. All patients demonstrated improvement in vascular resistance by tourniquet test when given these hormones but the platelet response was variable. Only 4 revealed any increase in platelets during preoperative therapy but 5 patients showed partial or complete remission after splenectomy. The latter 5 included 2 subjects who failed to respond to ACTH with platelet increases. In addition, no type of endocrine effect on platelets could be found to yield pre-

* We are grateful to Dr. Lawrence E. Young, Rochester, N.Y., for performing these special tests to help determine the type of hemolytic anemia.

dictable splenectomy results. Of 3 patients having no platelet increase from pre-operative ACTH, 2 had complete remissions, while one relapsed after splenectomy. Similarly, a complete remission during ACTH therapy in 2 patients was followed by only a partial remission after splenectomy in one and complete remission in another.

Discussion. This study again illustrates that the hemostatic defect in idiopathic thrombocytopenic purpura is twofold: The platelet deficiency which is irregularly corrected by adrenal hormones and vascular fragility which is regularly improved by these hormones. This concept has previously been advanced by Faloon *et al.*[10]. A complete review of the theories of the pathogenesis of idiopathic thrombocytopenic purpura has been presented recently[19].

Hanlon[13] has stated that there was no exact parallel between cases in which there was a response to adrenal hormones and a similar response to splenectomy. This study confirms that conclusion. However, since all patients

TABLE 1.—SUMMARY OF VASCULAR AND PLATELET RESPONSE TO PRE-OPERATIVE ACTH AND TO SPLENECTOMY IN 7 PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA

	Response to Pre-op. ACTH		*Response to Splenectomy*	
	Vascular	*Platelets*	*Vascular*	*Platelets*
Patient 1 (M. H.)	Complete	None	Complete	Complete
Patient 2 (B. E.)	Complete	Partial	Relapse	Relapse
Patient 3 (B. H.)	Complete	Complete	Complete	Complete
Patient 4 (M. B.)	Complete	None	Relapse	Relapse
Patient 5 (J. K.)	Complete	None	Complete	Complete
Patient 6 (C. D.)	Complete	Partial	Complete	Complete
Patient 7 (H. Z.)	Complete	Complete	Partial	Partial

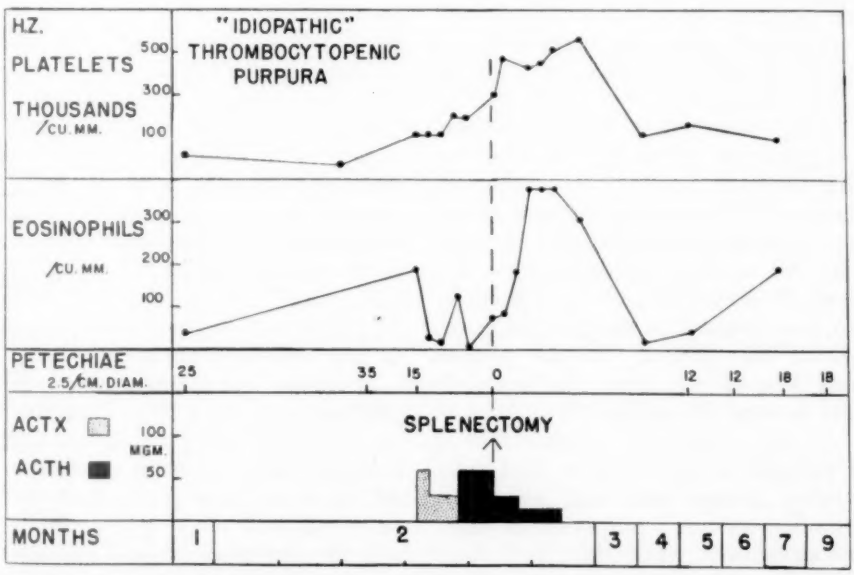


Fig. 7.— Excellent platelet response to ACTH but only partial remission after splenectomy in Patient 7. Note the variable time periods in abscissa to allow greater detail.

showed improvement in capillary fragility, this lack of correlation does not detract from the usefulness of ACTH or cortisone in controlling acute episodes whether subsequent splenectomy is elected or not. The use of these hormones before and during splenectomy does not appear to alter the final result, for without these hormones such surgery affords incomplete or no relief of symptoms in as many as one-third of the patients following splenectomy[15,34]. However, in spite of the large number of failures after surgery, splenectomy should be carried out in adults who do not improve after a trial of expectant treatment, since spontaneous remissions seem to occur in only about one-third of all patients with this disease.

Several reports from Ragan and his coworkers[2,6,26-28] have indicated that humans or animals who are receiving ACTH or cortisone show a retardation of wound healing. Conway and Stark[5] recently reported another patient with Cushing's disease who showed delay in epithelization. Modern has stated[22] that surgical intervention should not be planned while the patient is on ACTH or cortisone. However, several recent reports[7,8,23,29,33] indicate that on ordinary therapeutic dosage of these hormones, the problem of interference with wound healing is negligible. Thorn *et al.*[32] have emphasized on the basis of work by Findlay and Howes[11] that the marked differences in the effect of adrenal steroids on wound repair may depend on the state of nutrition of the patient. In the present study none of the 7 patients had difficulty in wound healing.

In 1937, Wintrobe[34] reported that of 24 patients from his clinic and from 4 other clinics who had idiopathic thrombocytopenic purpura, 5 died postoperatively. Most that died were in an acute hemorrhagic state. More recent reports show less operative mortality probably from a combination of factors such as better operative technique, better understanding and treatment of surgical shock, and so on. Coller *et al.*[4] reported 4 deaths in 41 patients who had splenectomy for idiopathic thrombocytopenic purpura. Of the 38 patients studied by Hirsch and Dameshek[15] who had splenectomy, 3 died. One of these had "thrombocytopathic" thrombocytopenia, and the other 2 were operated on during episodes of severe purpura. Robson[30] reported 19 patients who were splenectomized with no mortality. Lahey and Norcross[18] reported 17 cases and Cole *et al.*[3] 26 cases, all with no operative mortality. Zollinger *et al.*[36] reported one death in 57 splenectomies for idiopathic thrombocytopenic purpura, this occurring in a 70-year old woman with pneumonia and extensive cerebral hemorrhage prior to operation.

It has been indicated by all authors that the performance of emergency splenectomy during an acute bleeding episode will carry a high operative mortality. Since the adrenal hormones may control the acute hemorrhagic episodes in this disease, it is now possible to prepare the patient preoperatively so that surgical risk is lessened. Furthermore, because these hormones do not seem to be detrimental to wound healing, it seems reasonable to administer them routinely pre-operatively. If splenectomy fails, these hormones may be useful in controlling hemorrhagic symptoms, as was necessary with Patient 2.

Summary and Conclusions. 1. Seven patients with idiopathic thrombocytopenic purpura were studied as to their vascular and platelet response to ACTH or cortisone pre-operatively and then followed after splenectomy.

2. Pre-operative adrenal cortical hormone administration or stimulation regularly improved capillary fragility

but irregularly produced a rise in the platelet count.

3. Response of platelets to ACTH pre-operatively was no indication as to whether splenectomy would yield a permanent remission.

4. None of these patients presented any operative difficulties nor any retardation of wound healing.

5. Pre-operative administration of these hormones seems justified in order to reduce surgical complications.

REFERENCES

1. **Bethell, F. H., Meyers, M. C., Miller, S.,** and **Bullock, W. H.**: Trans. Assn. Am. Phys., **64**, 199, 1951.
2. **Blunt, J. W., Jr., Plotz, C. M., Lattes, R., Howes, E. L., Meyer, K.,** and **Ragan, C.**: Proc. Soc. Exp. Biol. & Med., **73**, 678, 1950.
3. **Cole, W. H., Walter, L.,** and **Limarzi, L. R.**: Ann. Surg., **129**, 702, 1949.
4. **Coller, F. A., Blain, A., III,** and **Andrews, G.**: Indications for and Results of Splenectomy. Springfield, Ill., Charles C Thomas, 1950.
5. **Conway, H.,** and **Stark, R. B.**: Plastic and Reconst. Surg., **8**, 354, 1951.
6. **Creditor, M. C., Bevans, M., Mundy, W. L.,** and **Ragan, C.**: Proc. Soc. Exp. Biol. & Med., **74**, 245, 1950.
7. **DeKruif, H.,** and **Baker, N. H.**: Minnesota Med., **34**, 1092, 1951.
8. **Ellison, E. H., Martin, M. C., Williams, R. R., Clatworthy, H. W., Hamwi, G.,** and **Zollinger, R. M.**: Ann. Surg., **134**, 495, 1951.
9. **Evans, R. S.,** and **Liu, C. K.**: Arch. Int. Med., **88**, 503, 1951.
10. **Faloon, W. W., Greene, R. W.,** and **Lozner, E. L.**: Am. J. Med., **13**, 12, 1952.
11. **Findlay, C. W., Jr.,** and **Howes, E. L.**: New Eng. J. Med., **246**, 597, 1952.
12. **Ham, T. H.**: A Syllabus of Laboratory Examinations in Clinical Diagnosis, p. 225. Cambridge, Mass., Harvard University Press, 1950.
13. **Hanlon, D. G.**: Proc. Staff Meeting Mayo Clinic, **27**, 273, 1952.
14. **Harrington, W. J., Sprague, C. C., Minnich, V., Moore, C. V., Ahlvin, R. C.,** and **Dubach, R.**: Ann. Int. Med., **38**, 433, 1953.
15. **Hirsch, E. O.,** and **Dameshek, W.**: Arch. Int. Med., **88**, 701, 1951.
16. **Jacobson, B. M.,** and **Sohier, W. D.**: New Eng. J. Med., **246**, 247, 1952.
17. **Kaznelson, P.**: Wien. klin. Wchnschr., **29**, 1451, 1916.
18. **Lahey, F. H.,** and **Norcross, J. W.**: Ann. Surg., **128**, 363, 1948.
19. **Lozner, E. L.**: Am. J. Med., **14**, 459, 1953.
20. **Meyers, M. C., Miller, S.,** and **Bethell, F. H.**: J. Lab. & Clin. Med., **36**, 965, 1950.
21. **Meyers, M. C., Miller, S., Linman, J. W.,** and **Bethell, F. H.**: Ann. Int. Med., **37**, 352, 1952.
22. **Modern, F. W. S.**: Ann. West. Med. & Surg., **5**, 153, 1951.
23. **Olsen, A.**: Acta endocrinol., **9**, 1, 1952.
24. **Pilot, M. L.**: Am. J. Clin. Path., **20**, 870, 1950.
25. **Pohle, F. S.**: Am. J. Med. Sci., **197**, 40, 1939.
26. **Ragan, C., Grokoest, A. W.,** and **Boots, R. H.**: Am. J. Med., **7**, 741, 1949.
27. **Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K.,** and **Blunt, J. W.**: Proc. Soc. Exp. Biol. & Med., **72**, 718, 1949.
28. **Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K., Blunt, J. W.,** and **Lattes, R.**: Bull. New York Acad. Med., **26**, 251, 1950.
29. **Robinson, H. S., Palmer, R. A., Bagnall, A. W.,** and **McIntosh, H. W.**: Canadian Med. Assn. J., **66**, 347, 1952.
30. **Robson, H. N.**: Quart. J. Med., **18**, 279, 1949.
31. **Stefanini, M., Santiago, E. P., Chatterjea, J. B., Dameshek, W.,** and **Salomon, L.**: J. Am. Med. Assn., **149**, 647, 1952.
32. **Thorn, G. W., Jenkins, D., Laidlaw, J. C., Goetz, F. C., Dingman, J. F., Arons, W. L., Strecten, D. H. P.,** and **McCracken, B. H.**: New Eng. J. Med., **248**, 323, 1953.
33. **Weisman, P. A., Quinby, W. C., Jr., Wight, A.,** and **Cannon, B.**: Ann. Surg., **134**, 506, 1951.
34. **Wintrobe, M. M., Hanrahan, E. M., Jr.,** and **Thomas, C. B.**: J. Am. Med. Assn., **109**, 1170, 1937.
35. **Wintrobe, M. M., Cartwright, G. E., Palmer, J. G., Kuhns, W. J.,** and **Samuels, L. T.**: Arch. Int. Med., **88**, 310, 1951.
36. **Zollinger, R. M., Martin, M. M.,** and **Williams, R. D.**: J. Am. Med. Assn., **149**, 24, 1952.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.

JOHN RHEA BARTON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

AND

C. G. JOHNSTON, M.S., M.D.

PROFESSOR OF SURGERY, WAYNE UNIVERSITY
DETROIT, MICHIGAN

RECENT ADVANCES IN THE KNOWLEDGE OF THE MECHANISM, DIAGNOSIS AND TREATMENT OF HEAD INJURY

BY E. S. GURDJIAN, M.D.

AND

J. E. WEBSTER, M.D.

(From the Department of Surgery, Wayne University College of Medicine and the University Neurosurgical Service, Grace Hospital, Detroit, Michigan)

DURING the past decade, advances have been made in our knowledge of the mechanism, the diagnosis and the treatment of head injury. During World War II, the principles evolved from experiences in World War I were utilized and a practical demonstration of what could be done with penetrating wounds of the brain was given. Undoubtedly, the use of sulfonamides and antibiotics also helped. Research done during the past decade has clarified the mechanism of skull fracture and concussion. The utilization of new diagnostic procedures including electroencephalography and angiography with a more vigorous search for hemorrhagic collections by operative intervention has evolved. Advances have continued in the surgical management of penetrating wounds since World War II. Intracerebral hematomas are now frequently sought and found in penetrating wounds of the brain. Reports in the literature from the Korean War concerning intracerebral hematomas show that a search for this lesion may save lives (Barnett[1]). The management of penetrating wounds involving the paranasal sinuses has become standardized (Webster, Schneider and Lofstrom[36]; Webster and Gurdjian[35]; Botterell and Stewart[3]; Bishop[2]). Vascular injuries involving the venous channels and dural sinuses are being successfully managed (Meirowsky[27]). In the next few pages an attempt will be made to summarize this more recent information under the headings (1) Studies on the Mechanism of Head Injury,

(2) Diagnostic Studies in Head Injury and (3) Newer Concepts in the Treatment of Head Injury.

Mechanisms of Head Injury. A head injury may result from a direct blow caused by a moving object striking the head or by indirect blow caused by the moving body and head becoming suddenly stopped or decelerated by a non-moving or slower moving object. Whether by the direct or indirect application of force, certain physical changes take place. These include deformation (compression) or inbending of the skull by the blow with either a sudden setting of the head into motion (acceleration) or, a sudden stoppage of the head (deceleration) (Denny-Brown and Russell[9]). In the ordinary case of head injury compression and acceleration and compression and deceleration usually co-exist or develop in rapid succession. In a direct blow, injury to the head alone is most likely, whereas, in an indirect injury, there is a likelihood of damage also to other parts of the body (Gurdjian and Webster[17]). Furthermore, in indirect injuries, the head does not have to touch a non-moving or slower object. The actual sudden setting of the head to motion may initiate physical forces that result in intracranial damage. The so-called whip lash injuries of the head and neck (Gay and Abbott[13]) and the injuries of the head in a fall with the lower parts of the body striking a non-moving object are examples of indirect forces acting upon the head.

Mechanism of Skull Fracture. The velocity of the injuring force is responsible for the type of fracture produced. The faster the blow, the greater the likelihood of depression or perforation; and the slower the blow, the greater the likelihood of generalized deformations of the skull (Gurdjian, Webster and Lissner[19]). With the use of the "stresscoat", the deformations of the skull following impact have been evaluated. It has been found that with a low velocity blow, an area of inbending occurs at the point of impact. This area of inbending rebounds if the force of the blow is not severe enough to cause comminution at the point of impact. Simultaneously, with the inbending at the area of impact, there are evidences of outbending in regions of the skull in close proximity to the area of inbending. A linear fracture is usually initiated in the area of outbending in close proximity to the area of inbending about the point of impact. The fracture line then extends towards the point of the blow and in the opposite direction. The point of blow attracts the fracture line since, as it rebounds, it becomes an area of stress concentration. Consequently, the fracture line extends toward the point of the blow; thus, linear fractures are the result of distant stresses and arise at a point away from the area of impact and extend toward the point of impact and in the opposite direction (Gurdjian and Lissner[15]; Gurdjian, Webster and Lissner[20]). The experimental use of "stresscoat" has also revealed that distant areas of deformation occur in the skull (Gurdjian, Webster and Lissner[21]). For instance, in the forward portions of the vertex and at the interparietal regions, blows result in deformations in the roof of the orbit on one or both sides. Such deformations and stresses may result in distant fractures. Fractures have been frequently seen in penetrating war wounds with no connection between the distant fracture and the area of penetration (Campbell[6]; Johnson and Dutt[24]).

In the dry skull it has been shown that a blow of a steel pellet traveling at 50 ft./sec. results in a linear fracture. The same steel pellet traveling at 90 ft./sec. (when dropped from the tenth floor of a building down an elevator shaft) results in a clear perfor-

ation of the skull. The importance of the velocity of the blow in local deformations and local failure cannot be over emphasized. In high velocity wounding, after certain speeds, the missile actually imparts radial acceleration to the tissues it contacts. Consequently, a tremendous explosive force is produced as the bullet or the shrapnel traverses the brain. These concepts are presented in the work of Zuckerman[38] in England, and Butler, Puckett, Harvey and McMillen[5] in this country, who show that, when a pellet pierces a paraffin cube and passes through it, the latter swells to several times the original dimensions. In living experiments it has been found that an actual cavity forms about the pellet and this cavity is fifty or more times the size of the missile. It is probably produced by a vaporizing effect. The presence of such a cavity around the missile explains why the bullet path may be distant to the shattered femur or other bony structures. The bullet itself may be several centimeters away from the edge of the bone, but the pressure from the large cavity around the missile exerts a shattering force. In high velocity wounding the importance of complete debridement of the wound becomes apparent, since a core of tissue is destroyed as the missile passes through the brain. This core of tissue may be centimeters thick, depending upon the velocity of the missile. The higher the velocity, the greater the area of damage, and the greater the need for complete debridement of the missile tract. The missile tract may contain foreign particles, debris and shattered pieces of bone, all of which, of course, are completely removed by modern neurosurgical methods and equipment (Webster and Gurdjian[35]; Campbell[6]).

A study of the intracranial pressure changes following experimental head injury with quantitative determinations of acceleration and pressure have been made by the present authors[18]. By a use of the accelerometer prepared by the Stathem Company, acceleration of the head in numbers of G have been recorded in experimental injury. It has been found that the magnitude of acceleration is not as important as its time duration. Concussive effects expressed in a sudden rise in blood pressure and an apnea with or without a loss of the corneal reflex, have been obtained with accelerations of as high as 650 G. and as low as 250 G. The time duration of the acceleration appears to be in direct ratio to the degree of clinical effects. Sudden accelerations produce damage in the cranial cavity by producing increase in intracranial pressure. Deformations of the skull also result in increase in intracranial pressure. The greater the time duration, the more serious the clinical results. It has been found that when the head is free to move there is a pressure gradient in the cranial cavity with higher pressures at the point of impact and with lower and negative pressures in the opposite side of the head. When the head is not free to move and deformation of the skull is the main result of the injury, then there is an increase in pressure throughout the cranial cavity usually of equal proportions. It appears, therefore, that in the case of a compression concussion there is a sudden rise in pressure which is present throughout the cranial cavity. In an acceleration or deceleration type of injury, there are oscillating changes in pressure in various parts of the cranial cavity. As a result of the latter, mass movements in the cranial cavity occur (Pudenz and Sheldon[29]). It must be, of course, emphasized that it is impossible to have an acceleration injury without some compression effect because of the inertia of the head or the object struck. The pressures recorded in concussive blows in the experimental

animal are of the order of from 20 to 100 pounds per square inch, or 1000 to 5000 mm. of mercury. In more recent experiments it has been observed that, by varying the time duration of the pressure, a concussive effect of moderate degree may be obtained with a pressure of 20 pounds per square inch lasting 1/30 sec., or 65 to 70 pounds per square inch lasting 1/1000 sec. Special devices which produce pressures for such short periods of time are to be described in the near future.

Compression, acceleration and deceleration result in measurable pressure changes within the cranial cavity. With deceleration and acceleration, mass movements of the brain may occur, with tear of the tissues resulting in secondary changes such as hemorrhage. In the final analysis, the effects upon the brain are caused by the changes in pressure in the intracranial cavity, whether these changes are produced by deformation of the skull *per se*, or by sudden setting of the head into motion, or its sudden stoppage (Gurdjian and Webster[17]).

Immediately following the activity of these forces there is an increased activity of the electrical emissions of the brain (Walker, Kollros and Case[32]) followed by a depression which lasts for several seconds or minutes. In this connection, Walker, Kollros and Case have suggested that a concussive effect is comparable to an epileptic fit with increased electrical activity of the neurones resulting from an injury to the cell membranes. However, it has also been shown that immediately following an impact the convulsive re-activity of the brain is definitely lowered. Groat, Magoun, Dey and Windle[14] have shown that the electrical re-activity of the supranuclear motor system is impaired immediately following an experimental concussion. Spiegel, Spiegel-Adolph, Wycis and Marks[31], discussing cerebral concussion and convulsive re-activity, state that immediately following a concussive blow generalized convulsions induced by previously injected metrozol in rats ceased. The injection of atropine in doses able to prevent the effect of acetylcholine upon the electrical activity failed to forestall the interruption of the convulsive activity by the concussive blows. The same authors showed that the oxygen uptake in rat brains by means of the Warburg technique failed to demonstrate significant differences between normal and concussed animals. The lactic acid content of cerebral tissue and phosphorylation cycle metabolites were found at normal levels in concussed animals by Gurdjian and Stone[16]. However, Gurdjian, Webster and Stone[22] have found that lactic acid has increased and ADP and phosphocreatine are decreased in contusions and bruises of the brain. A brief period of impairment of the cellular surface membrane immediately following impact was thought to be present in measurements of the polarizability of the brain, according to Spiegel, Spiegel-Adolph, Wycis and Marks[31]. Certain enzymatic substances able to split nucleic acid and to produce chromotolytic changes in the anterior horn cells *in vitro* could be demonstrated in the cerebrospinal fluid of the patients and experimental animals following cerebral concussion. In normal controls, such substances were not present or were present in only minimal quantities. Thus, these authors theorize that following cerebral trauma, one not only has a brief period of transitory cellular semipermeable membrane injury, but also longer lasting disturbances of intracellular metabolic processes.

Diagnostic Studies. Among the diagnostic studies, in addition to the usual clinical and neurological examination, the use of the electroencephalogram has become standardized (Dow, Ulett, and Raaf[10]; Jasper, Kershman and El-

vidge[23]). Dawson, Webster and Gurdjian[7] found that the electroencephalogram sometimes showed little or no abnormality, in spite of brain injury, soon after trauma. In fatal cases the records were quite normal at first in some patients except for certain focal changes. Slow activity occurring within the first 48 hours almost invariably foretold a fatal outcome. Severely injured patients had progressive slowing, and disorganization of the electroencephalographic activity was a grave sign if present within the first 48 hours. Delayed generalized suppression was not of prognostic value. In patients with subdural hematomas, suppression over the area of hematoma was more important in the early case than the presence of a delta focus. The use of the electroencephalogram in the more chronic cases of head injury has become valuable. In many patients with chronic subdural hematoma, lateralization of the lesion is possible in about 50 to 75% of the cases.

It is interesting to note that in some instances of head injury, the record deteriorates, although the patient's clinical condition may ameliorate. In other instances the record may improve even though neurological deficits are present.

Neurosurgical diagnostic studies for the evaluation of intracranial mass lesions following head injury have often been both unsuccessful and dangerous. Air studies frequently are unsuccessful because of the increase in intracranial pressure present in these acute cases. Recently angiography has been used to advantage, although it, too, carries some degree of danger. It has been possible by the means of carotid angiography to delineate mass lesions that involve the anterior two-thirds of the cranial cavity, particularly as concerns intracerebral lesions. Webster, Dawson and Gurdjian[34] and Kristiansen[25] have shown that by the use of angiography, particularly under local anesthesia, such masses can readily be identified and operated upon successfully.

The more vigorous search for intracranial mass lesions with exploration of various parts of the head has been discussed and subscribed to by Echlin[11] and Lemmen and Schneider[26] and others. The indications for intervention include increasing drowsiness and coma, with localizing and focal signs not previously present, suggesting intracranial hemorrhagic collection. The use of survey Roentgen studies of the skull would delineate a shifted pineal, if the pineal shadow is present, and the use of the electroencephalogram in some of these patients may be worthwhile.

Treatment. Under medical treatment, Ward[33] suggests the use of atropine or parasympathetic paralyzing agent in order to counteract the presence of acetylcholine in the spinal fluid in the seriously injured cases of head injury. Since the electroencephalographic pattern after injury can be abolished by appropriate doses of atropine sulfate in experimental animals, this drug was given in quantities of 0.1 mg. per kilogram of body weight. This implies an average dose of about 1/10 of a grain in the adult. In some patients dramatic results were obtained by the use of atropine.

The use of sulfonamides and antibiotics has been of major value in the management of open wounds and in cerebrospinal fluid leakage from the cranial orifices. The use of these drugs to control meningitis is well known. These drugs also make possible surgical procedures in patients who ordinarily would have succumbed to the first attack of meningitis.

During the past decade progress has been made in the treatment, both in civilian as well as military cases of head injury. In the civilian group a better understanding of the patient

with acute and subacute subdural hematomas and those with intracerebral hematomas has evolved. Many of these cases are now operated upon with good results. The large series of cases reported by Browder[4] and Echlin[11] indicate these advances. More thorough and meticulous methods have been adopted in dealing with penetrating wounds, particularly including cases with paranasal sinus involvement, reducing inflammatory complications, such as meningitis and brain abscess. Tears of vascular channels, including dural sinus tears, can now be successfully treated by blood replacement, aided by the newer hemostatic agents as oxycel, gelfoam, and others. Tracheotomy in patients who have difficult and labored breathing has been life-saving in many instances. Such a procedure is simple and should be carried out in an admitting room when respiratory obstruction is evident.

Increased intracranial pressure resulting in herniation of the temporal lobes against the brain stem, with serious sequelae, has been studied by Ryder and Evans[30]. With this particular problem in mind Munro[28] and his group suggest incision of the tentorium in order to relieve the pressure against the brain stem and the posterior fossa structures. Unfortunately, as yet, the experience is not conclusive to suggest a wider use of such decompressive operations.

The efforts of engineers and physicians to bring about safety measures for counteracting the effects of impact should be commended (Gamble and Shaw[12]; Wood, Lambert and Baldes[37]). The work of DeHaven[8] suggests that the majority of severe injuries occur, not because of the initial impact, but rather because the victim is thrown about in a vehicle following the initial impact. Measures providing a slow deceleration of the body will make it possible for the human to withstand a considerable number of G's without fatality. By contributions of this type directed at counteracting the effects of impact, future accidents of land and air may cease to be catastrophic.

REFERENCES

(1) **Barnett, J. C.**: Intracranial hematomas associated with penetrating wounds of the brain. Read before the Harvey Cushing Society, April 24, 1953, at Hollywood, Florida. (2) **Bishop, E.**: Penetrating wounds involving the air sinuses. Ibid. (3) **Botterell, E. H.**, and **Stewart, O. W.**: Brit. J. Surg. (War Surg. Supp. No. 1), **112**, 1947. (4) **Browder, J.**: Bull. New York Acad. Med., **19**, 169, 1943. (5) **Butler, E. G., Pickett, W. O., Harvey, E. N.**, and **McMillen, J. H.**: J. Neurosurg., **2**, 358, 1945.

(6) **Campbell, E.**: High velocity mechanisms. Read before the Harvey Cushing Society, April 24, 1953, at Hollywood, Florida.

(7) **Dawson, R. E., Webster, J. E.**, and **Gurdjian, E. S.**: J. Neurosurg., **8**, 613, 1951. (8) **DeHaven, H.**: War Med., **2**, 586, 1942. (9) **Denny-Brown, D.**, and **Russell, W. R.**: Brain, **64**, 93, 1941. (10) **Dow, R. S., Ulett, G.**, and **Raaf, J.**: Electroencephalographic studies immediately following head injury. Read before the 99th Annual meeting, American Psychiatric Assn., Detroit, Michigan, May 10-13, 1943.

(11) **Echlin, F.**: J. Neurosurg., **6**, 294, 1949.

(12) **Gamble, J. L.**, and **Shaw, R. S.**: Fed. Proc., **6**, 109, 1947. (13) **Gay, J. R.**, and **Abbott, K. H.**: The common whiplash injuries of the neck. To be read before the 102nd Annual Meeting of the Am. Med. Assn., in New York, June, 1953. (14) **Groat, R. A., Magoun, H. W., Dey, F. L.**, and **Windle, W. F.**: Am. J. Physiol., **141**, 117, 1944. (15) **Gurdjian, E. S.**, and **Lissner, H. R.**: Surg., Gynec. & Obst., **83**, 219, 1946. (16) **Gurdjian, E. S.**, and **Stone, W. E.**: Fed. Proc., **5**, 38, 1946. (17) **Gurdjian, E. S.**, and **Webster, J. E.**: A. Res. Nerv. & Ment. Dis., Proc. (1943), **24**, 48, 1945. (18) **Gurdjian, E. S., Lissner, H. R., Latimer, F. R., Haddad, B. F.**, and **Webster, J. E.**: J. Neurol., **3**, 417, 1953. (19) **Gurdjian, E. S., Webster, J. E.**, and **Lissner, H. R.**, J.

Neurosurg., **7**, 106, 1950. (**20**) Iidem: Radiology, **54**, 313, 1950. (**21**) Iidem: Ibid. **60**, 226, 1953. (**22**) **Gurdjian, E. S., Webster, J. E.,** and **Stone, W. E.**: War Med., **6**, 173, 1944.

(23) **Jasper, H., Kershman, J.,** and **Elvidge, A.**: A Res. Nerv. & Ment. Dis., Proc. (1943), **24**, 388, 1945. (**24**) **Johnson, R. T.,** and **Dutt, P.**: Brit. J. Surg. (War Surg. Supp. No. 1), 141, 1947.

(25) **Kristiansen, K.**: Surg., **24**, 755, 1948.

(26) **Lemmen, L. J.,** and **Schneider, R. C.**: J. Neurosurg., **9**, 245, 1952.

(27) **Meirowsky, A. M.**: Wounds of dural sinuses. Read before the Harvey Cushing Society, April 24, 1953, at Hollywood, Florida. (**28**) **Munro, D.**: Personal communication.

(29) **Pudenz, R. H.,** and **Sheldon, C. H.**: J. Neurosurg., **3**, 487, 1946.

(30) **Ryder, H. W.,** and **Evans, J. P.**: Newer concepts of the role of increased intracranial pressure in head injury. Read before the Harvey Cushing Society, April 24, 1953, Hollywood, Florida.

(31) **Spiegel, E. A., Spiegel-Adolph, M., Wycis, H. T.,** and **Marks, M.**: A. Res. Nerv. & Ment. Dis., Proc. (1946), **26**, 84, 1947.

(32) **Walker, A. E., Kollros, J. J.,** and **Case, T. J.**: Ibid., **24**, 437, 1945. (**33**) **Ward, A. A., Jr.**: J. Neurosurg., **7**, 398, 1950. (**34**) **Webster, J. E., Dawson, R.,** and **Gurdjian, E. S.**: Ibid., **8**, 368, 1951. (**35**) **Webster, J. E.,** and **Gurdjian, E. S.**: Internat. Abst. Surg., **82**, 353, 1946. (**36**) **Webster, J. E., Schneider, R. C.,** and **Lofstrom, J. E.**: J. Neurosurg., **3**, 329, 1946. (**37**) **Wood, E. H., Lambert, E. H., Baldes, E. J.,** and **Code, C. F.**: Fed. Proc., **5**, 327, 1946.

(38) **Zuckerman, S.**: Brit. Med. J., **2**, 131, 1940.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100.

OPHTHALMOLOGY

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.

AND

HENRY P. WAGENER, M.D.
SECTION OF OPHTHALMOLOGY, MAYO CLINIC
ROCHESTER, MINNESOTA

OPHTHALMOLOGIC DIAGNOSIS OF MENINGIOMAS OF THE SPHENOIDAL RIDGE

BY THOMAS P. KEARNS, M.D.

AND

HENRY P. WAGENER, M.D.
SECTION OF OPHTHALMOLOGY,
MAYO CLINIC, ROCHESTER, MINNESOTA

MENINGIOMAS constitute approximately 15% of all intracranial tumors. Cushing and Eisenhardt[2] found an incidence of 13.4% in their group of 2,203 tumors of the brain. Meningiomas occur most frequently in the parasagittal region, the sphenoidal ridge being the next most common anatomic site. Castellano, Guidetti and Olivecrona[1] found 608 meningiomas among 3,256 verified tumors of the brain (18.6%). One hundred eleven of the meningiomas took their origin from the sphenoidal ridge (18.25%). Petrohelos and Henderson[5] found 7 meningiomas of the sphenoidal wing among 358 tumors of the brain (1.9%).

Since the symptoms presented by meningiomas of the sphenoidal ridge are often ocular, the burden of recognition and early diagnosis frequently rests upon the ophthalmologist. For this reason it was felt that a review of the incidence and symptomatology of this condition might be of interest.

AGE DISTRIBUTION. Intracranial meningiomas are rare in childhood and in old age, although one of Cushing and Eisenhardt's[2] patients was 8 and another was 86 years old at the time of admission. They found that the average age of women with meningiomas was 42.9 years and that of men was 52 years at the time of admission to the hospital. However, the average age of onset of symptoms was about the same in both men and women, namely approximately 38 years. In the series of pterional meningiomas "*en plaque*" reported by Castellano, Guidetti and Olivecrona[1], the youngest patient was 17 and the oldest 63 on admission, the average age being 47 years. The average duration of symptoms before admission was 4 years. In Cushing and Eisenhardt's[2] series of meningiomas of the sphenoidal ridge, the ages of the patients ranged from 26 to 67 years. Groff[3] reported a series of cases in which he found a 26-year-old Negress with a meningioma arising from the sphenoidal ridge. Elsberg, Hare and Dyke[4] reported a case of proptosis due to meningioma apparently arising from the sphenoidal ridge in a 19-year-old girl. MacCarty and Gogela[7] reported a case of meningioma of the sphenoidal ridge in a boy 12 years of age which

they thought might be the youngest age on record for such a lesion.

Sex Distribution. It is generally recognized that meningiomas occur more commonly in women. Cushing and Eisenhardt[2] found the ratio to be 6 to 4 in favor of women. They also pointed out that the occurrence in certain loci is largely restricted to women. Uihlein and Weyand[11], in a recent series of meningiomas of the anterior clinoid process found that 39 of 52 patients were females. In the 25 pterional tumors *en plaque* reported by Castellano and co-workers[1], there were 19 females and 6 males. All of Cushing and Eisenhardt's[2] 16 pterional tumors *en plaque* were in females.

It is postulated that some hormonal influence accounts for this difference. Further evidence for hormonal influence is the observance of the development of a meningioma during or shortly after pregnancy. Cushing and Eisenhardt[2] noted this, and more recently Weyand, MacCarty and Wilson[13] have described such cases. In 2 meningiomas removed while the patients were pregnant, the latter authors found the cytoplasm of the cells foamy and swollen, which might have been the result of increase in the intracellular fluid. This could explain an increase in size of the tumor during pregnancy and a decrease after termination of the pregnancy. Rand and Andler[9] reported a verified meningioma of the sphenoidal ridge which had been present during two pregnancies and deliveries. It seemed significant that during both pregnancies the symptoms from the tumor increased. They expressed the opinion that the patient had a disturbance of water balance, with increased tissue fluid due to retention of sodium.

Lateralization of the Tumors. Although the ocular symptoms are the same regardless of the side of the lesion, the general symptoms may differ. Tumors of the left ridge more often have psychosis and other mental changes as part of their symptomatology than do tumors of the right ridge. This probably is explained on the basis of involvement of the dominant hemisphere. For the same reason, removal of a meningioma of the left sphenoidal ridge is likely to prove more hazardous than the removal of a right-sided lesion.

In Cushing and Eisenhardt's[2] series of 53 meningiomas of the sphenoidal ridge, the tumor was on the right side in 30 cases and on the left side in 23 cases. Elsberg, Hare and Dyke[4] reported 15 cases of proptosis due to intracranial tumors, most of which were meningiomas. They found that the exophthalmos occurred more frequently on the left side in females (7 of 8) and more frequently on the right side in males (5 of 7). Smith[10] expressed the opinion that meningiomas *en plaque* occur more often on the left side than on the right.

Anatomic Considerations. The sphenoidal ridge represents the anatomic dividing line between the anterior and the middle cranial fossae. According to Horning[6], the sphenoidal ridge is the name given the horizontal bony protuberance formed by the lesser and greater wings extending laterally from the anterior clinoid process, fanning out on its lateral extension to join the pterional region of the cranial vault. This bony ridge is in close proximity to the orbit and to the structures entering and leaving the orbit by way of the optic canal and the superior orbital fissure. It is this anatomic proximity that accounts for the high incidence of ocular symptoms.

Cushing and Eisenhardt[2] divided the sphenoidal ridge into three arbitrary zones for purposes of tumor localization. The inner or deep ridge is the portion nearest the sella and adjacent to the anterior clinoid proc-

ess. It overlies the superior orbital fissure and the cavernous sinus. The middle or alar portion includes the middle third of the ridge. These inner two thirds of the ridge roughly correspond to the lesser wing of the sphenoidal bone. The outer or pterional portion is adjacent to the lateral wall of the cranial vault and corresponds to the flaring margin of the greater wing of the sphenoid. This classification has merit in that tumors present different symptoms depending on the locations along the ridge. For instance, a tumor along the inner part of the ridge is more likely to produce a field defect, since it is closer to the optic nerve and optic chiasm than is one located farther out along the ridge. Exophthalmos and temporal swelling are more often associated with pterional tumors. It is in this area that meningioma *en plaque* develops. This is a flat spreading tumor which is accompanied by considerable hyperostosis of bone with involvement of the orbital walls, and hence by considerable proptosis of the globe in many cases.

Ocular Symptomatology of Previously Reported Cases. Cushing and Eisenhardt[2] described the symptoms in their series after first classifying the anatomic location along the sphenoidal ridge. The characteristic onset of their 13 tumors along the inner part of the ridge was that of unilateral failure of vision associated with primary atrophy of the optic nerve which often progressed to near blindness before the other eye became involved. In 8 of these 13 cases the homolateral eye was blind on admission. Unilateral proptosis was present in 9 cases. Contralateral papilledema occurred in the majority of cases. The authors stated that because of the invariable unilaterality of these tumors it appeared that they are more prone to evoke the Foster Kennedy syndrome than are tumors of the olfactory groove, which are often median in position. Oculomotor palsies were present in the majority of cases.

There were 11 tumors of the middle ridge in their series. The outstanding finding of this group was bilateral papilledema which was naturally more advanced on the side of the lesion. There was a slowly progressive contralateral homonymous hemianopsia in one case.

Twenty-nine of the tumors of their series were of the outer ridge, 16 being pterional tumors *en plaque* and 13 being global tumors. Tumors of the *en plaque* group produced hyperostosis chiefly of the greater wing of the sphenoid which in turn produced a slowly increasing unilateral exophthalmos with ultimate impairment of vision and palpable swelling in the temporal region. In 15 of the 16 cases of pterional tumors *en plaque*, there was exophthalmos while in 10 there was palpable swelling. Ten of the patients had loss of vision, but only 2 were blind in the homolateral eye. The global tumors characteristically expanded into the sylvian fissure, which caused bilateral papilledema in 12 of the 13 patients of this group; exophthalmos was present in only 4.

Walsh[12] has called attention to the fact that the characteristic syndrome in tumors of the inner part of the ridge is unilateral loss of visual acuity with homolateral optic atrophy and defects in the visual field. There are minimal roentgenographically visible changes in the sella turcica. Exophthalmos and paralysis of the ocular muscles develop later, the lateral rectus being the most frequently involved muscle. He has stated that tumors of the middle part of the ridge are characterized by their lack of ocular signs. In cases of *en plaque* tumor of the outer part of the ridge, exophthalmos is the earliest symptom, and loss of visual acuity is a late symptom.

Elsberg and Dyke[3], in their report of 4 cases of tumor of the mesial part of the sphenoidal ridge, said that "by studies of the visual fields and by the recognition on Roentgen films of changes in the basal cisterns after encephalography, growths in this situation can be diagnosticated when they are small." Their 4 patients were adults whose main or only complaint consisted of a slowly progressive diminution of vision in one eye. They noted that the other symptoms which usually occur in intracranial growths were conspicuous by their absence.

Groff[5], in a discussion of 9 cases of meningiomas of the lesser wing of the sphenoid bone, stated that the clinical picture usually begins with unilateral loss of vision, and that it is a prominent and progressive symptom throughout the course of the disease. He also stated that exophthalmos may precede the visual disturbances and that later symptoms develop referable to the structures in close relationship to the lesser wing of the sphenoid bone.

Smith[10], in discussing the syndrome of pterional meningioma *en plaque*, listed the following characteristics: (1) slowly progressive, painless, nonpulsating unilateral exophthalmos, (2) normal vision, fields and eyegrounds, (3) suprazygomatic fullness, (4) Roentgen findings of hyperostosis involving the sphenoid ridge, the greater and lesser wings of the sphenoidal bone, the roof of the orbit and the area where the frontal and parietal bones articulate with the greater wing of the sphenoidal bone (pterional region), (5) occurrence usually in women of middle age and (6) greater incidence of the tumor on the left side.

In Castellano, Guidetti and Olivecrona's[1] series, all 25 of the *en plaque* tumors were associated with exophthalmos, and in 11 this was the initial symptom. Impairment of sight was present in 15 cases, and it was the initial symptom in 4 cases. They stated that a diagnosis of pterional meningioma *en plaque* is supported by the following points: (1) occurrence usually in women of middle age, (2) history of a slowly developing exophthalmos with ultimate impairment of vision on the affected side, (3) temporal swelling and (4) Roentgen findings of hyperostosis involving the sphenoidal ridge, the greater and lesser wing of the sphenoidal bone and the roof of the orbit.

Comment. Because of our interest in the differential diagnosis of intracranial lesions involving the optic nerves and visual pathways, it was thought worth while to review the ophthalmologic lesions observed in 106 surgically and pathologically verified meningiomas of the sphenoidal ridge from the files of the Mayo Clinic. The ophthalmologic features of these tumors will be considered in some detail.

It is often difficult for the neurosurgeon to be certain just where along the sphenoidal ridge the tumor actually arises. This is particularly true if the tumor is large, vascular and associated with much hyperostosis of bone. As there is considerable overlapping of the ocular manifestations of meningiomas involving the various segments of the sphenoidal ridge, the neuro-ophthalmologic symptoms and signs will be discussed as they were presented by this group of meningiomas as a whole.

STATISTICAL DATA. The youngest patient of our series was a woman 25 years old, while the oldest was a man 64 years old. The average age for the group as a whole was 47.2 years, the male patients averaging 50.1 years and the female patients averaging 48 years.

The sex ratio showed the usual preponderance of females, there being 76 women to only 30 men. Therefore 71.7% of these patients were women.

which agrees very favorably with the 75.4% found in Cushing and Eisenhardt's[2] series.

The lateralization in our series indicated that the right side was affected more often than the left. Sixty-one (57.6%) of the tumors were of the right ridge while 45 (42.4%) were of the left ridge. This 57.6% incidence, and Cushing and Eisenhardt's 56.6% incidence for the right-sided tumors, seem to indicate that there is a slight predilection for the right sphenoidal ridge.

OCULAR SYMPTOMS. Seventy-three of the 106 patients in the present series had disturbance of the eyes as the only, or one of the chief complaints. These complaints were loss of vision, increased prominence of one eye, double vision, pain around one eye and swelling of the lids. The remaining 33 patients complained of headache, convulsions and mental changes. It is interesting to note that of these 33 patients in whom eye symptoms were not noted, 15 had choked disks, 7 had pallor of one or both disks, 3 had pupillary abnormalities and one had a significant field defect. This leaves only 7 patients of the entire 106 without eye findings.

VISION AND FIELDS OF VISION. Central vision was recorded and the visual fields were plotted for all patients except 7 in whom poor general condition or lack of co-operation did not permit such subjective testing. Sixty-three of the patients were found to have loss of vision in one or both eyes which could be attributed to the tumor. Most commonly there was a slowly progressive unilateral loss of vision. Many of the patients were able to date the onset of loss of vision five to ten years prior to the date of examination. Unilateral loss of vision always lateralized the tumor. If both eyes were involved, the tumor was, without exception, on the same side as the eye with the greater loss of vision.

The most frequent type of field defect was that of a prechiasmal lesion of one optic nerve. Nineteen were blind in one eye at the time of admission. Sixty of the patients had localizing field defects, of which 39 (65%) were unilateral and 21 (35%) were bilateral. Of the 21 bilateral defects, 13 were variants of the bitemporal type and 8 were homonymous. Three of the patients had nonlocalizing field defects (binasal contraction of secondary optic atrophy). In 7 of the patients, visual fields were not determined for the reasons mentioned above. The remaining 36 patients had normal visual fields.

PROPTOSIS. The most common ocular complaint next to visual loss was proptosis. Thirty-four of the group exhibited this finding. The position of the eyes was determined with the Hertel exophthalmometer. The degree of proptosis varied between 2 and 19 mm., with an average of 5.9 mm.

The proptosis was usually straight forward, or straight forward and downward. It was nonreducible, and in most of the cases it was not associated with pain. It was slowly progressive and, like the loss of vision, often dated back many years.

There are two mechanisms for the production of proptosis in meningiomas of the sphenoidal ridge. Both were present in some of the cases. One mechanism is that the tumor may extend into the orbit in a dumbbell fashion and hence produce the exophthalmos of an orbital tumor. In other instances, exophthalmos may be produced without an actual extension into the orbit, through the development of hyperostosis of bone in the walls of the orbit. In several cases these were first considered to be primary orbital tumors until Roentgen-ray or other evidence disclosed their true nature.

PAPILLEDEMA. In 46 of the cases there were choked disks (bilateral in 31 and unilateral in 15). The papille-

dema varied from mild edema of one disk margin with only slight elevation, to 6 diopters of elevation of each nerve head. In the majority of cases in which papilledema was present, there was an elevation of 2 to 4 diopters.

Of the patients with unilateral choked disk the intracranial lesion was homolateral with the papilledema in 10. It was contralateral in 5 patients, representing examples of the Foster Kennedy syndrome, since all 5 of these patients also had pallor of the homolateral disk. This syndrome is usually diagnostic of a basofrontal lesion but is rather rare. In the presence of this syndrome, a meningioma of the sphenoidal ridge should be suspected, in the absence of an abnormality of the sense of smell.

The patients with unilateral papilledema homolateral to the meningioma often present a puzzling diagnostic problem. With the associated loss of vision, an acute optic neuritis is suggested. Two of the patients of this series were first considered to represent cases of optic neuritis, until other findings pointed to the proper diagnosis. Observation of the pupillary reactions is often helpful in distinguishing the unilateral papilledema caused by a meningioma of the sphenoidal ridge. A dilated pupil resulting from associated involvement of fibers of the third nerve by the tumor does not respond to either direct or consensual light. A dilated pupil which does not contract to direct light as a result of acute optic neuritis reacts promptly to consensual light from the fellow eye. The visual field defects may be quite similar and are of little help in differentiating the two conditions. The onset and mode of progression of the loss of vision should be rapid in cases of optic neuritis and gradual in cases of tumor, but in some instances the history may be misleading in this respect.

There seem to be two mechanisms responsible for the development of choked disks in meningiomas of the sphenoidal ridge. Unilateral homolateral papilledema probably results from local venous engorgement caused by direct pressure of the tumor at the orbital apex, by obstruction in the orbit as suggested by Walsh[12], or else from pressure on the cavernous sinus. Bilateral papilledema or unilateral contralateral papilledema is a manifestation of increased intracranial pressure. The presence of both mechanisms in the same patient might be expected to cause a greater degree of papilledema on the side of the tumor. However, this expectation is not borne out by the findings in the present series. In 13 of the patients with bilateral papilledema, the elevation was the same in both eyes; it was greater in the homolateral eye in 9 cases and greater in the contralateral eye in 9 cases. This is another demonstration of the fact that the mechanism of production of choked disks is not as yet understood.

PALLOR OF THE DISKS. Forty-two of the patients were found to have pallor of one or both disks. In 34, the pallor was unilateral and on the same side as the tumor. The 5 patients falling in the category of the Foster Kennedy syndrome are included in this group. The 8 patients with bilateral pallor of the disks were all found to have chiasmal types of field defects, indicating that the tumor had spread toward the midline to involve the optic chiasm and the contralateral optic nerve. The pallor varied from slight lightness in color, that could be detected only by close comparison with the fellow eye, to the grade-4 pallor of complete optic atrophy. The pallor paralleled the loss of vision fairly closely in all cases.

Pallor of the disks may be secondary to previous papilledema as a result of secondary optic atrophy. However, pallor of primary optic atrophy is more

commonly found in patients with this type of tumor. It is produced by direct pressure on the optic nerves by the tumor and is usually associated with a field defect.

PUPILLARY CHANGES. Pupillary abnormalities were observed in most of the patients with advanced pallor of the disks and loss of vision. In only one patient was unilateral dilatation of the pupil the only ocular finding. In this case the electroencephalogram raised the suspicion of a tumor, and a pneumoencephalogram and craniotomy confirmed the diagnosis. Meningioma of the sphenoidal ridge must be a rather rare cause of isolated dilatation and sluggishness of the pupil.

PARALYSIS OF OCULAR MUSCLES. Only 15 of the group were noted to have definite weakness of extraocular muscles. In 8 of these the limitations of rotation were not due to involvement of the cranial nerves, but were secondary to proptosis, and were due rather to the abnormal position of the eye. Among the 7 patients with paresis actually due to involvement of cranial nerves, were 4 patients with involvement of the sixth nerve, one with involvement of the third nerve, one with involvement of the third and sixth nerves, and one with involvement of the third and fourth nerves. Walsh[12] also found, as stated previously, the sixth nerve to be most frequently affected. If the patients with limitation of motion associated with proptosis are excluded, abnormalities of the extraocular muscles are not a frequent finding in meningiomas of the sphenoidal ridge.

ROENTGENOGRAPHIC CHANGES. Roentgenograms of the heads of all patients were made as a part of the routine investigation. Although the tumor itself is not visualized, the presence of calcification in the tumor or the associated osteomatous thickening of adjacent bone leads to a diagnosis in many cases.

The roentgenograms of the head were reported as negative in only 24 of the 106 patients. Of the 82 patients with reports of abnormalities, a diagnosis of meningioma of the sphenoidal ridge was suggested in 53 on the basis of Roentgen-ray findings alone. This represents exactly 50% of the total group of patients, and is a surprisingly high percentage. Most of the reports were of diffuse osteomatous thickening in the region of the wings of the sphenoid. The other abnormalities reported were erosion and destruction of the sella, decalcification of the anterior clinoid processes, and enlargement of the sella from increased intracranial pressure. Three of the patients had enlargement of the optic foramen on the side of the tumor, although not all the patients were sent for special views of the optic foramina.

It is thus evident that the roentgenogram plays a very important part in the diagnosis of these tumors. Every patient with an orbital tumor and any patient with unusual "optic neuritis" should undergo roentgenographic examination of the head, to help rule out or establish the diagnosis of meningioma of the sphenoidal ridge.

A COMPOSITE CASE. When a large series of cases is reviewed, it is always interesting to postulate the usual and more typical findings in one composite hypothetical case. In the presence of a tumor of the sphenoidal ridge, such a patient (1) is more likely to be a woman in her forties or fifties, (2) will have noticed a gradual protrusion of the right eye over a number of years, (3) will have had loss of vision over a long period either preceding, following or coinciding with the proptosis, (4) will have no history of pain although there may be headaches, (5) will have pallor of the disk, (6) will have a field defect suggesting a prechiasmal lesion, (7) may have choked disks and (8) will present, on roent-

genographic examination of the head, a diffuse osteomatous thickening in the greater and lesser wings of the sphenoid.

Summary and Conclusions. In addition to a review of the more recent literature, an analysis and discussion of the data on 106 patients with surgically and pathologically proved meningioma of the sphenoidal ridge are presented.

Loss of vision is the most common ocular finding and the complaint that most frequently brings the patient for examination. Proptosis is the next most common complaint. Papilledema often occurs in these patients and it is frequently unilateral. Pallor of the disk may be found and the Foster Kennedy syndrome may be present.

A definite diagnosis of meningioma of the sphenoidal ridge may be suggested by a roentgenogram of the head, since osteomatous thickening of the bone is often present.

Since the presenting symptoms of this type of tumor are mainly ocular, the ophthalmologist is often the first one to be consulted by these patients. An early diagnosis helps lead to neurosurgical cure.

REFERENCES

(1) **Castellano, F., Guidetti, B.,** and **Olivecrona, H.**: J. Neurosurg., **9**, 188, 1952. (2) **Cushing, H.,** and **Eisenhardt, L.**: Meningiomas; Their Classification, Regional Behaviour, Life History, and Surgical End Results. Springfield, Illinois, Charles C Thomas, 1938, 785 pp.
(3) **Elsberg, C. A.,** and **Dyke, C. G.**: Arch. Ophth., n.s., **12**, 644, 1934. (4) **Elsberg, C. A., Hare, C. C.,** and **Dyke, C. G.**: Surg., Gynec., & Obst., **55**, 681, 1932.
(5) **Groff, R. A.**: Arch. Ophth., n.s. **15**, 163, 1936.
(6) **Horning, E. D.**: Sphenoidal Ridge Meningiomas. Thesis, Graduate School, University of Minnesota, 1949.
(7) **MacCarty, C. S.,** and **Gogela, L. J.**: J. Neurosurg., **6**, 182, 1949.
(8) **Petrohelos, M. A.,** and **Henderson, J. W.**: Tr. Am. Acad. Ophth., **55**, 89, 1950.
(9) **Rand, C. W.,** and **Andler, M.**: Arch. Neurol. & Psychiat., **63**, 1, 1950.
(10) **Smith, J. W.**: Arch. Ophth., n.s. **22**, 540, 1939.
(11) **Uihlein, A.,** and **Weyand, R. D.**: Arch. Ophth., **49**, 261, 1953.
(12) **Walsh, F. B.**: Clinical Neuro-ophthalmology. Baltimore, Williams & Wilkins Co., 1947, 1532 pp.
(13) **Weyand, R. D., MacCarty, C. S.,** and **Wilson, R. B.**: S. Clin. North America, 31, 1225, 1951.

PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MAY 19, 1953

Post-tetanic potentiation in intact human skeletal muscle. S. Y. BOTELHO, M.D., and L. CANDER, M.D. (Dept. of Physiology and Pharmacology, Grad. School of Med., Univ. of Penna.). It has long been known that in animals post-tetanus single twitches develop greater tension than pre-tetanus single twitches. Various investigators have given evidence that this post-tetanic potentiation of single twitch tension results from changes of the muscle itself rather than from changes in nerve conduction or neuromuscular transmission in the absence of neuromuscular block. Since no objective studies of post-tetanic potentiation have been made in man, we have begun a study of this phenomenon in order to determine the factors which alter the post-tetanus state both in normal and diseased muscle.

We have found that in seven normal human subjects, the tension of a single twitch after a tetanus of 30/sec. for one second may increase to as much as 125% of the pre-tetanus single twitch tension. This post-tetanic potentiation of single twitch tension reaches a maximum within the first minute after tetanus and gradually falls toward the pre-tetanus value, but is still present at least ten minutes after the tetanus. The increase in single twitch tension after the tetanus is accompanied by a decrease in latent period of contraction, which reaches a minimum of 63% of the pre-tetanus value by the first minute after tetanus, gradually rises toward the pre-tetanus value and is still present at least 10 minutes after the tetanus. There is also a slowing of the rate of contraction, which is greater early in the contraction period, but which returns to the pre-tetanus value by the third to fifth minute after tetanus. These changes in the single twitch after tetanus, are abolished by 10 minutes of ischemia produced by circulatory arrest. The extinction of the post-tetanus changes is not the result of a decrease in temperature which may accompany ischemia of long duration since we found that muscle temperature did not decrease more than 2.35° C during the 10 minutes of ischemia.

The Action of Ouabain on the Papillary Muscle Using a New Respirometer Allowing Simultaneous Recording of Contraction. KWANG SOO LEE, Ph.D. (Dept. of Pharmacology, Jefferson Medical College). The action of ouabain was investigated on the papillary muscle using a new respirometer which enables us to observe both the oxygen consumption and the contraction of muscle.

This new method utilizes two new pieces of apparatus. One is a modified Warburg flask with built-in-platinum electrodes and the other is a muscle holder with a mirror attached for recording the contraction of the muscle.

Examination for the validity of this method was made using Hill's formula, and it was concluded that this method is adequate for the respiration of papillary muscles.

Cat papillary muscles were prepared from the right ventricle. The oxygen consumption and the contraction stabil-

ized after an initial rapid fall. Various concentrations of ouabain were added to the medium during this period of stabilization.

At all concentrations used, a gradual increase in the contractility began immediately following the addition of the drug and continued until contracture appeared.

The oxygen consumption increased with the onset of contracture and arrhythmia, reaching about 200% in 3 hours.

This result appears to support the claim by others that ouabain increases the contractility of the muscle by increasing the utilization of energy and not by increasing the production of energy. However, the possibility that ouabain may increase the force of contraction by promoting the production of energy through other mechanism than aerobic metabolism is not excluded.

This action of ouabain on the heart muscle is compared with that of l-epinephrine which shows a distinctly different pattern of response.

Some Observations on the Carotid Body Blood Flow in the Cat. M. DE BURGH DALY, M.B., B. CHIR., C. J. LAMBERTSEN, M.D., and The Late A. SCHWEITZER, M.D. (Dept. Physiol., University College, London, and Dept. Pharmacol., Univ. Penna. Med. Sch.) On the basis of previous anatomical studies on the carotid body blood supply, a technique has been devised for collecting the venous effluent from the carotid body with its natural arterial blood supply intact. The average blood flow at normal arterial blood pressure is 38 c.mm./min. (range 22 to 55 c.mm./min.), which is smaller than that obtained previously by less exact methods (J. Physiol., **117**, 12P, 1952). If the blood pressure is reduced by bleeding, the control carotid body blood flow diminishes until, at 40 to 50 mm. Hg, it is zero. Occlusion of the ipsilateral common carotid artery diminishes the carotid body blood flow, as does electrical stimulation of the cephalic end of the cut cervical sympathetic nerve; intravenous injections of epinephrine, 10 to 25 μg., increase it Samples of blood drawn simultaneously from the femoral artery and from the cannula draining carotid body blood show no significant A-V O_2 difference at normal arterial blood pressure. This would be in keeping with the high rate of blood flow. If, however the flow is reduced to 9 c.mm./min. by lowering the blood pressure, an A-V O_2 difference of 2 vols. per cent then becomes apparent. This is equivalent to not more than 80% oxygen saturation of hemoglobin in carotid body venous blood. By calculation from the Fick equation, the oxygen consumption is 0.00018 cc. O_2/min./carotid body. Although no change in arterial blood pO_2 occurs on lowering the blood pressure, others have shown a marked increase in the impulses in chemoreceptor fibers. It is apparent that anoxemia within the carotid body may occur in the presence of a normal arterial pO_2 simply by virtue of the slow passage of blood through the organ. Blood flow through the carotid body is, therefore, an important factor in determining the activity of the chemoreceptors.

The Postsynaptic Source of the Negative Intermediary Potential. GEORGE M. AUSTIN, M.D., and GRAYSON P. MCCOUCH, M.D. (Depts. of Surgery and Physiology, Univ. of Penna. Med. Sch.). Originally described in 1933, the negative intermediary potential (hereafter called NIP) is recorded from the dorsum of the cord following stimulation of a dorsal root or peripheral nerve. It has been described from various sources by different authors. Gasser believes it is due both to the discharge of interneurons and their axons. Hughes, McCouch, and Stewart described it as arising from in-

terneurons. The work of Barron and Matthews suggests the depolarization of terminal branches of primary fibers as the etiology. Campbell concluded that the source was the after-potential of the primary afferent fibers of the dorsal column. Lloyd and McIntyre believe the source of part of the NIP is activity in primary afferent fibers. Recent investigations on cat and monkey have given us additional evidence for the postsynaptic source of this potential. Briefly enumerated, it follows: Often at threshold for the intramedullary spike potential (hereafter called ISP) there is no sign of any NIP. After spinal transection there is progressive fall in threshold for the NIP with no change in the ISP. Following spinal transection the threshold NIP appears at a lower threshold, and associated with a threshold polysynaptic reflex instead of a threshold monosynaptic reflex as recorded in the decerebrate state. During asphyxia there is a progressive fall in height and increase in latency of NIP, in spite of a rise in height, and no change in latency, of ISP. During asphyxia with complete disappearance of the NIP, though the height of ISP has begun to fall, it is still above that of the control before asphyxia. After spinal transection a conditioning stimulus from internal saphenous nerve will completely inhibit the NIP from gastrocnemius; whereas, prior to transection in the decerebrate state, this did not occur. We conclude from these results that the source of the NIP is postsynaptic.

BOOK REVIEWS AND NOTICES

THE ESOPHAGUS AND ITS DISEASES. By EDDY D. PALMER, M.D., Lt. Col., Medical Corps, U. S. Army; Chief, Gastrointestinal Section, Walter Reed Army Hospital. Pp. 553; 95 ills., and 24 Colored Plates. New York: Paul B. Hoeber, Inc., 1952. Price, $15.00.

THIS book is an engagingly written, well printed, and attractively bound compendium of the principal existing knowledge on the esophagus and its disorders. Despite the broadness of the subject, the field is comprehensively covered and the presentations are clear and to the point. In attaining conciseness some sketchiness in places has been inevitable. Where this is apparent, however, it is relatively minor and does not seriously detract from the completeness of the discussion.

The fact that the book is essentially an abridgement of what has been written about the esophagus and its diseases removes from it the element of personal viewpoint and experience. This may prove disappointing for students of the subject who seek to enrich their knowledge by the experience of others. For those who may wish a concise and impersonal presentation of what is currently known about the esophagus and its diseases, however, this treatise should prove valuable.

J. B.

INTRACRANIAL ANEURYSMS. By WALLACE B. HAMBY, M.D., Prof. Neurological Surgery, University of Buffalo. Pp. 564; 104 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $14.25.

THE author's purpose "is to assemble in one volume enough of the data on intracranial aneurysm to allow the reader to get a comprehensive grasp of the subject." Since the author is a surgeon he has "emphasized treatment which at present is surgical".

The book is divided into seven chapters as follows: 1) The Cerebral Circulation; 2) General Considerations; 3) Diagnosis of Intracranial Aneurysms; 4) Intact Intracranial Aneurysms; 5) Ruptured Intracranial Aneurysms; 6) Arteriovenous Aneurysms; 7) General Remarks Concerning Intracranial Vascular Surgery.

Dr. Hamby has drawn freely on his own contributions and has quoted extensively the experiences of others. The thorough bibliography will be of great help to those interested in further studies of this problem.

Although this book will be useful to the medical profession at large, it is particularly valuable to the neurosurgeon who realizes the pitfalls and the dangers in intracranial vascular surgery.

M. S.

METHODS IN MEDICAL RESEARCH. VOL. 5. Edited by A. C. CORCORAN. Pp. 394; 92 ills Chicago: Year Book Publishers, Inc., 1952 Price, $7.50.

FIFTY-SIX contributors and reviewers participated in the preparation of the fifth volume of this series. Section I is entitled "Methods for Separation of Complex Mixtures and Higher Molecular Weight Substances," and includes excellent chapters on the subjects of countercurrent distribution, paper chromatography, electrophoresis, and ultracentrifugation.

Section II, "Methods of Renal Study," is devoted to descriptions of numerous procedures applicable to studies of human, as well as animal, kidney physiology and pathology.

The third and last section deals with "Immunochemical Methods for Determining Homogeneity of Proteins and Polysaccharides."

Those interested in clinical and laboratory investigation in the above fields will find this volume a valuable tool.

C. Z.

DISEASES OF METABOLISM. Edited by GARFIELD G. DUNCAN, M.D., Director of Medical Division, Pennsylvania Hospital, Philadelphia. 3rd ed. Pp. 1179; 212 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $15.00.

THE encyclopedic character of this text provides a wealth of material for the physician and student interested in metabolic disorders. This new edition includes contributions by several recognized authorities not found in the previous editions; namely, Drs. Rawson and Rall, P. White, Keys, Soskin and Levine, Watson and others. The remaining co-authors have rewritten the sections for which they were previously responsible. The chapters on Water Balance by Peters and Vitamins by Spies and Butt are excellent and thorough presentations. It is interesting to note that most of the authors have published much of the material in their respective chapters elsewhere in monographs and essays already recognized as outstanding in con-

temporary medical writing. This book is regarded as a complete and authoritative source of data relating to metabolic disease from both the clinical and investigative points of view.

C. S.

OPHTHALMIC PATHOLOGY, AN ATLAS AND TEXTBOOK. Compiled by various staff members of the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology. Pp. 489; 260 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $18.00.

THIS volume is a combination textbook and atlas. The text was written by Jonas S. Friedenwald, Helenor Campbell Wilder and A. Edward Maumenee with special sections by Theodore E. Sanders, John E. L. Keyes, Michael J. Hogan, and William C. and Ella U. Owens. The atlas is a compilation of photographs which appeared earlier in the first three editions of the atlas of ophthalmic pathology plus a considerable amount of new material. The book is intended for use by the ophthalmologist who wants to understand the mechanism and morphology of the diseases of his specialty and for the general pathologist who finds this field so difficult because of a paucity of material. It is difficult to imagine how the book could be improved in any way.

The volume opens with sections concerned with the gross and microscopic anatomy and the normal physiology of the various components of the eye. The next several chapters deal with the general pathology of the region such as aging, the specific and non-specific inflammatory processes and traumatic injury. Following this there are chapters on the diseases peculiar to each anatomic part of the ocular tract with final sections on congenital anomalies, degenerative diseases and tumors. Each section includes several pages of text followed by numerous incomparable photographs.

As one reads the text one is impressed with the comprehensive coverage with an admirable sense of elimination of all unnecessary detail. It represents a really fine job of editing. The photographic material is the product of the oldest registry in the institute and has the advantage of several revisions in the earlier atlases. These are the most beautiful illustrations on this subject that this reviewer has ever seen. The combination of text and atlas accomplishes its purpose as few books have ever done. It should be in every ophthalmologist's office and every pathologist's library.

E. A.

PRACTICAL DERMATOLOGY. By GEORGE M. LEWIS, M.D., F.A.C.P., Cornell University Medical College. Pp. 328; 99 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $7.50.

DR. LEWIS' book is intended for medical students' instruction, for the guidance of general practitioners, and as an aid for orientation of other specialists. Its 328 pages encompass descriptions or brief mention of most of the cutaneous processes, adequate details in therapy, both topical and systemic, plus a formulary index and a satisfactory general index. For the interested reader there is a useful bibliography. The material is presented in a well balanced fashion. Dr. Lewis, a prominent student of dermatologic mycology, has devoted only 23 pages to the fungus infections of the skin. Because of its decreasing importance, syphilis is accorded 11 pages. Aside from the concise descriptions, the outstanding feature of this volume is the collection of well chosen and well reproduced illustrations. Although the author has emphasized the value of certain laboratory studies such as biopsies, it is regrettable that a discussion of the basic sciences is omitted. In spite of this, Dr. Lewis has made a real contribution to the textbooks on Dermatology.

H. B.

NUTRITION AND DIET IN HEALTH AND DISEASE. By JAMES S. MCLESTER, M.D., Professor of Medicine Emeritus, University of Alabama and WILLIAM J. DARBY, M.D., PH.D., Professor of Biochemistry and Director of Division of Nutrition, Vanderbilt University. 6th ed. Pp. 710; 14 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $10.00.

THE new and largely rewritten edition of this well-known authoritative text has been kept abreast of the rapidly advancing field of nutrition with the assistance of a collaborator whose work in this subject is widely recognized. The book is complete in every detail with ample discussions of current knowledge concerning the many food factors of importance in human nutrition. One may question the value of including clinical descriptions of disease entities since they are necessarily abbreviated in a text of this type; however, this presentation aids in the correlation of the specific disease with dietary measures advocated in its management. The separation of the chapter on deficiency diseases from the fundamental description of the vitamins involved seems unwarranted. The contributions of Dr. Jeans on Feeding of Infants, Dr. Lund on Nutrition in Surgery, and Dr. Goodhart on Nutrition in Industry

are extremely valuable to readers with interests in these aspects of nutrition.

The appendix presents basic data on methods of feeding and food processing, and contains complete tables on food composition. The careful study of this volume will provide the physician, teacher and student with a sound understanding of principles and practices of modern nutrition. C. S.

ZINSSER'S TEXTBOOK OF BACTERIOLOGY. Edited by DAVID T. SMITH, M.D., and NORMAN F. CONANT, PH.D. Duke University School of Medicine. 10th ed. Pp. 1012; 328 ills. New York: Appleton-Century-Crofts, Inc., 1952. Price, $11.00.

THE latest edition of this standard text is a significant improvement over the previous one. No longer are there numerous and lengthy literature references cluttering up the text material. A considerable amount of technical detail has been deleted or transferred to the Appendix. Together with a briefer treatment of many of the basic bacteriologic phenomena of prime interest only to professional microbiologists, these changes have contributed much toward making this a highly readable volume for students of medicine and allied fields. It is also an excellent reference book for the clinician.

One wonders why so much space is devoted to Pijper's work on flagella, and to a highly detailed discussion of the nature of viruses; also why the Koch postulates are not presented early in the text or listed in the index. Although minor errors, such as the use of "allergin" for "allergen" (page 213), and contradictions, such as in desensitization to tuberculin (page 215), do occur, the content is on the whole accurate and carefully presented.

Especially helpful are the excellent illustrations and adequate references. By maintaining a balance between basic bacteriologic approach and clinical application the authors have provided us with a valuable "Introduction to the Infectious Diseases." E. S.

INTRODUCTION TO PHYSIOLOGICAL OPTICS. By ARMIN VON TSCHERMAK-SEYSENEGG, University of Munich. Pp. 282; 111 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $10.50.

THIS book is a translation from the German by Dr. Paul Boeder. It fills a need by supplying information about the Physiology of Vision which is not easily available in the English literature. The book deals with the whole act of vision. This work should be of help to everyone interested in Physiological Optics. Chapters are included on the optical image, introduction to light sense and color sense. There is also an introduction to Uniocular Space Sense. Binocular Space Sense is well treated. The chapter on the introduction to the physiology of ocular movements is extremely well done. M. O.

NEUROSURGERY IN GENERAL PRACTICE. By ADRIEN VER BRUGGHEN, M.B., CH.M., M.S., F.A.C.S., Clinical Professor of Neurological Surgery, (Rush) University of Illinois College of Medicine. Pp. 665; 282 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $14.00.

THIS book has been written for the general practitioner by an outstanding neurosurgeon who was one himself. Dr. Ver Brugghen "talks directly" to the reader and develops the diagnosis and treatment of the various neurosurgical conditions in a concise and easily understandable manner. His advice is further clarified by pertinent case reports, each followed by a short comment. The illustrations are profuse, clear and are well correlated with the text.

The conditions which are most commonly seen by the general practitioner are developed thoroughly. For example, head and spinal cord injuries are described in six separate chapters covering 136 pages. An entire chapter is devoted to a complete understanding of the technique, therapeutics, contraindications, sequelae and fallacies of lumbar puncture. The other neurosurgical conditions are judiciously apportioned to the remaining chapters.

Ver Brugghen has purposely avoided any description of neurosurgical procedures. He has hoped that the book will help the general practitioner in deciding whether a patient presents a neurosurgical problem and how to get an "early proper disposition of the case." It is this reviewer's opinion that the author has not only done this but has also put together a text which will be of interest and help to the neurosurgeon. M. S.

PHYSICAL DIAGNOSIS. By HARRY WALKER, M.D., F.A.C.P., Prof. Clin. Med., Medical College of Virginia, Richmond. Pp. 461; 126 ills. St. Louis: C. V. Mosby Co., 1952. Price, $8.00.

DR. WALKER and his contributors have done a good job in the development of this text on physical diagnosis. The significant thing to the reviewer is that it is brief yet

completely covers the important phases of the subject. It should be a valuable part of the student's library. Approximately the first half of the book deals with methods of physical diagnosis. The latter half gives examples of various common medical disorders, in which physical signs are stressed under the headings of inspection, palpation, percussion, and auscultation. Of particular interest in this type of text are the chapters on the neurological and psychiatric examination which are complete yet proportionate to the over-all subject matter. This text is to be recommended. G. M.

MALADIES DES GLOBULES ROUGES ET DESORDRES ENDOCRINES. By A. ASCHKENASY. Pp. 112; 6 ills. Paris: G. Doin & Cie, 1952. Price, 700 fr.

THE large-scale use of cortisone and adrenocorticotropin in clinical medicine has brought increased interest in the hematologic effects of these and other hormones. Most of the emphasis, however, has been placed on the action of these substances on the eosinophil count and on leukemic processes. This review, which is concerned with the various endocrine influences on the erythrocytes, is, therefore, especially welcome. The discussion deals with erythropoiesis and hyposecretion and hypersecretion, respectively, of the hormones of the thyroid, the testes, the ovaries, the adrenals, and the pituitary.

The bibliography is extensive, comprising 535 references. Hematologists, endocrinologists, and internists who read French will find this work of interest. C. Z.

THE WHITE PLAGUE. TUBERCULOSIS, MAN AND SOCIETY. By RENE AND JEAN DUBOS. Rockefeller Institute for Medical Research. Pp. 277; 13 charts. Boston: Little, Brown and Co., 1952. Price, $4.00.

HERE at last is a book that considers Tuberculosis as it really is; not as a pulmonary disease, not as a systemic disease, not as an infection to be cured by chemicals or an anatomical anomaly to be treated by resection, but as a serious world-wide epidemic "the consequence of gross defects in social organizations and errors in individual behavior.

The authors, while eminently qualified to approach the subject from a purely "scientific" viewpoint, have chosen to examine the disease in the broadest way as a phenomenon of man's relations with his fellow-men, with the tubercle bacillus, and with his environment. "Physiological misery", be it due to the slums of the Industrial Revolution, the present economic status of large portions of the world's population, or the temporary dislocations of war, is considered the major factor in the production of Tuberculosis. Therefore, hope for eradicating the disease depends not only on public health measures to prevent the spread of tubercle bacilli but social measures to increase man's resistance to infection through a proper way of life.

Literate, lucid, and learned, this volume could be read with profit by anyone interested in the human race. R. C.

PHYSIOLOGIE NORMALE ET PATHOLOGIQUE DU METABOLISME DE L'EAU. By JEAN HAMBURGER AND GEORGES MATHE. Pp. 502; 53 ills. Paris: Editions Medicales Flammarion, 1952. Price, 2.85 francs.

THIS book is divided into three parts: Normal physiology, methods of investigation, pathology. The first part includes the various fluid compartments and their interchanges, water balance, water elimination by gastrointestinal tract, lungs, skin and kidneys, and endocrine control by pituitary, adrenal cortex and other glands. The second section considers methods for measurement of total body water, cellular and extracellular fluid, plasma volume and interstitial fluid. Osmotic pressure and studies on urinary elimination of water are also presented. Under pathology are found edema, dehydration and their relations to intra- and extracellular fluid. All material is extremely well organized and presented. The bibliography is very extensive. Those interested in this subject who can read French will find this book useful. M. O.

GRUNDRISS DER ELEKTROKYMOGRAPHIE. By K. HECKMANN, M.D., Munich. Pp. 36; 54 ills. Stuttgart: G. Thieme, 1952. (Grune & Stratton, Inc., New York, Agents for U.S.A.) Price, DM 6.60.

DR. HECKMANN'S experience in this field is 16 years old. Appropriate mention is made of the recent work in the U.S.A. by Henny, Boone, Chamberlain, Luisada, Fleischner, Rappaport, Ellinger, Gillick, and Schneider.

Registration of movements of selected points of the cardiovascular silhouette, as obtained in the anterior and both oblique views, with timing against the two heart sounds, is presented. First the findings under normal conditions are described. Thirty-one examples of abnormal graphs are given, descriptive and diagnostic.

By arranging the graphs obtained from different points of the cardiac surface in a co-

ordinate system, it becomes possible to construct isophases, that is, one obtains a spatial magnification of the whole process of motion. Graphs depicting what is normal, and 12 examples of abnormal conditions are given. Phase analysis permits, to some degree, a separate evaluation of actual pulsatory movements, and of pendulum movements, respectively. Phase analysis is also carried out for a horizontal plane of the heart; this permits study of the dorsal and ventral motion of the heart. H. R.

IMPLETOLTHERAPIE UND ANDERE NEURALTHERAPEUTISCHE VERFAHREN. By DR. MED. WALTER HUNEKE. Pp. 126; 12 ills. Stuttgart: Hippokrates-Verlag Marquardt & Cie, 1952. Price, DM 9.50.

THE author treats a great variety of conditions such as neuralgias, myalgias, arthritis, various types of headaches, epileptiform convulsions, psychoses, cardiovascular conditions, bronchial asthma, peptic ulcer, gynecologic diseases by injecting a novocaine—caffeine compound called impletol. He emphasizes the importance of the site of the injection. If a so-called focus is suspected in the tonsils or in the dental roots, the injection is made in their vicinity, in thoracic or visceral diseases in the corresponding dermatomes. He claims that a single injection often is able to produce a permanent cure within a second, and it is assumed that these therapeutic effects are due to an influence upon pathologic electrostatic conditions in the peripheral and central vegetative system. He admits that much depends on the personality of the physician. It seems, therefore, understandable that the author's optimism is not shared by the majority of his colleagues who emphasize the mystic element contained in this type of therapy. E. S.

SIDE EFFECTS OF DRUGS. By L. MEYLER, Consulting Physician at Groningen (Netherlands). Translated by Ph. Vuijsje and W. Mulhall Corbet, Amsterdam. Pp. 268. Houston: Elsevier Publishing Co., 1952. Price, $5.50.

SOME of the author's personal experiences led him to prepare this book on the harmful effects which can arise from the use of drugs. Practically every type of therapeutic agent is included, and the various toxic manifestations of each are listed. Unfortunately, the author was not able to consult the original articles in every case. As a result, the dosage causing toxicity is often not given. Indeed, the untoward reaction ascribed in some instances to one drug could well have been due to other prior or concomitant medication. Nevertheless, this is a worthwhile reference book and a timely reminder that the administration of any drug must be based on appropriate indications. C. Z.

PSYCHOANALYSIS AS SCIENCE. By ERNEST R. HILGARD, PH.D., LAWRENCE S. KUBIE, M.D., AND E. PUMPIAN-MINDLIN, M.D. Pp. 174, 7 ills. Stanford, California: Stanford University Press, 1952. Price, $4.25.

THIS lecture series delivered at the California Institute of Technology sets out to state the position and meanings of psychoanalysis midway in the twentieth century. Dr. Hilgard, Dean of the Graduate Division of Stanford University and formerly chairman of the Department of Psychology, discusses experimental approaches to psychoanalysis. He summarizes some of the recent experimental work testing the validity of psychodynamics in the laboratory.

Dr. Lawrence S. Kubie, clinical professor of Psychiatry and Mental Hygiene at Yale University, approaches the problem from the viewpoint of the clinician and indicates where psychoanalysis needs help from the exact sciences in making its concepts more precise and in developing more accurate instruments. Dr. Kubie makes a plea for a research institute in psychoanalytic psychology with active participation of the neurophysiologist, the biophysicist, the biochemist, pharmacologist, clinical psychologist, cultural anthropologist, biostatistician and psychoanalyst.

Dr. E. Pumpian-Mindlin, Chief of the Mental Hygiene Clinic of the Veterans Administration, Los Angeles, discusses the position of psychoanalysis in relation to the social and biological sciences. He shows how it takes into account both man's growth processes and his relations to the society in which he lives. He believes science cannot afford to overlook the important aspects of human activity that psychoanalysis attempts to investigate.

There is an index and a generous reference bibliography and the book is definitely recommended for any clinician interested in the emotional factor in disease. O. E.

DISEASES OF THE SKIN. A Manual for Students and Practitioners. By ROBERT M. B. MACKENNA, M.A.,M.D. (CAMB.), F.R.C.P. (LOND.); St. Bartholomew's Hospital and

Medical College, London. 5th ed. Pp. 611; 215 ills. London: Bailliere, Tindall and Cox; Baltimore: Williams and Wilkins Co., 1952. Price, $8.00.

DISEASES OF THE SKIN by MacKenna has gone through five editions since 1923 when the first edition was prepared by Robert W. MacKenna. This edition, by Robert M. B. MacKenna, represents one of the better British texts on Dermatology. The author has "endeavored to keep in mind the requirements of the medical student and the needs of the general practitioner." For the most part, an etiologic classification is followed in the presentation of the material. Corrections in terminology to conform to modern standards, excellent illustrations, reasonable integration of dermatology with other specialties of medicine, good but few references in the text, and few errors in typography comprise the essential features of this book. Since the author and publishers want a wide distribution of their production, it would help those outside the British Empire if certain preparations and instruments recommended were defined, (for example, Kilner hook). Also the use of penicillin locally is not to be condoned, (for example, penicillin cream, p. 81). H. B.

X-RAY DIAGNOSIS OF CHEST DISEASES. By COLEMAN B. RABIN, M.D. Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. Pp. 516; 288 ills. Baltimore: The Williams and Wilkins Company, 1952. Price, $12.00.

PUBLISHED previously as a section in Golden's Loose Leaf System of Diagnostic Roentgenology, this monograph has been reprinted in its entirety without alteration in content or form. As such it has encompassed the gamut of problems in the realms of thoracic disease, satisfactorily providing a background for roentgenologic evaluation of the normal and abnormal chest. The latter has been approached through a correlation of the pathologic findings with those portrayed roentgenographically.

The first part of the volume has been devoted to basic and general considerations including discussions of fluoroscopy, technical details, special examinations and anatomy of the bronchial tree. Two subsequent sections, comprising the major scope of this work have outlined in succession the roentgenologic appearance of single pathologic processes and the manifestations of various disease entities. The concluding part has been based upon the problems of differential diagnosis.

Emerging as a separate volume, this work has become more readily accessible to all physicians concerned with the diagnosis and treatment of chest disorders. Both the radiologist and his clinical colleagues should find this monograph of inestimable value. R. S.

CONGENITAL ANOMALIES OF THE HEART AND GREAT VESSELS. By MAURICE A. SCHNITKER, M.D., St. Vincent's Hospital, Toledo. Pp. 306; 19 ills. New York: Oxford University Press, 1952. Price, $8.00.

Two recent advances in medical science have made it mandatory for all practitioners of medicine to know the clinical aspects of the various types of cardiac anomalies. The application of surgical techniques makes accurate diagnosis necessary and cardiac catheterization and angiocardiograms make accurate diagnosis possible. In the foreword to this book, Dr. Thomas Durant points out the importance of initial recognition of the cases that they may be referred to the proper clinics for more detailed study and eventual treatment.

Dr. Schnitker's book takes up each developmental disturbance, defines it, explains the mechanism of its development and then discusses the morbid physiology which it induces. The anomalies are classified on the basis of their symptomatology. The entire plan of the book emphasizes the clinical diagnosis of these conditions. Where illustrations are helpful in explaining the text, pen drawings in black and white are used. All parts of the book are concise and clear, in its entirety there are only 300 pages of text. The author has not indulged in tedious accounts of pathogenesis but has given the essential features of each condition just as the clinician wants to know them. Dr. W. C. Pritchard has written the opening chapter on normal cardiac embryology. E. A.

GREAT ADVENTURES IN MEDICINE. EDITED BY SAMUEL RAPPORT AND HELEN WRIGHT, with an Introduction by DETLEV W. BRONK. Pp. 874. New York: Dial Press, 1952. Price, $5.00.

THIS compilation, which took more than 3 years to prepare, has fortunately strayed, (or so it seems to the Reviewer) from the original conception of collecting for the layman some of the most significant writings in the field of medicine. It now presents under one cover more than 70 selections not only of the actual writings of the very great, as in Osler's Bibliotheca Prima, but also includes medical fiction and essays about the very great, or about topics of first importance. Many of these es-

says were written by those who are great in their own right; all are held together by Synopses prepared by the Editors. The synopses, incidentally, are the weakest feature of the production, but could easily be improved in a second edition by transferring much of the biographical data to footnotes for each author, or to an addendum.

The text is divided into 6 Parts: 1, Introductory (brief and timeless); 2, Ancient and Medieval Times (67 pages); 3, The Rebirth of Medicine (106 pages); 4, Into Modern Times (290 pages); 5, The Turn of the Century and Beyond (208 pages); 6, Contemporary Medicine (147 pages). This chronologic arrangement, however, is followed only loosely at times, just as the material utilized has been loosely selected, both conducive to the benefit of the reader, however.

For we believe that this Omnibus, a more accurate title than Great Adventures, will provide pleasant bedtime reading as well as making classical texts conveniently available for reference in a way not provided by any other volume known to the reviewer. Who, for instance, would have readily available Aubrey's contemporary sketch of Harvey? Dr. Sangrado, Romeo's apothecary, Rab and his Friends, Sairey Gamp, George Weller's pharmacist mate doing an appendectomy on a submarine (which after all may be the truth and not mere fiction) are instances of entertaining pictures which illuminate the medical practice of their times; whereas excerpts from the Ebers papyrus, Leviticus, Galen, Boccaccio's Plague in Florence, Sydenham, Jenner's Enquiry, Koch on Tuberculosis, are but a few of the many that reproduce the actual words of the original observers. Though these are the most numerous of the various kinds of articles reproduced, it would have been preferable to have had more of the same, as compared with such selections as Fleming's article on Chemotherapy (rather than on Penicillin), Minot on Anemia (rather than on Pernicious Anemia), Engel's article in Harper's Magazine on Cortisone (and not Hench's original description), and so on.

It is hardly necessary to add that no such production could be expected to be satisfyingly adequate, nor that the selection made would be satisfying to all; they certainly are not so to the Reviewer. Yet he is glad to have the book available, and can think of no other medical anthology that would be entertaining and useful, even more than for the layman, to the medical student, practitioner or investigator, when he wants to get beyond the confines of his daily job and broaden his perspective and acquaintance with the general medical field. E. K.

MEDICAL CLINICS OF NORTH AMERICA. LOS ANGELES NUMBER, JULY, 1952. Pp. 291; 46 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $15.00 per annum.

THIS number is devoted to a symposium on Recent Advances in Medicine presented by physicians from the hospitals and from the University of Southern California School of Medicine in Los Angeles. Among the topics covered are recent developments in the therapy of edema, the prevention of coronary thrombosis, the prevention of atherosclerosis, the management of high blood pressure, the therapeutic use of quinidine, the diagnosis and management of hemorrhagic disorders, the effects of ACTH and cortisone in diseases of the digestive system, the management of atopic dermatitis, neurosyphilis and others. The articles are all of the usual high standard of excellence. R. K.

FUNCTIONAL NEUROANATOMY. BY WENDELL J. S. KRIEG, B.S. IN MED., PH.D., Professor of Anatomy, Northwestern University Medical School. 2nd ed. Pp. 659; approximately 300 figures. New York, Toronto: Blakiston Co., Inc., 1953. Price, $9.00.

IN the second edition of his well known text Dr. Krieg has increased the number of illustrations, rewritten the chapters on the cerebellum and cerebral cortex, and added substantially to the description of the gross anatomy of the brain.

Inclusion of the longitudinal sections of the brain stem in the atlas section of the book is a definite improvement, and the additional space devoted to the gross anatomy of the brain adds to the value of the book as a student text. It is to be regretted that the section dealing with the blood supply of the brain was not improved in the revision. D. K.

PROBLEMS OF CONSCIOUSNESS. TRANSACTIONS OF THE THIRD CONFERENCE. Edited by HAROLD A. ABRAMSON, M.D., Associate Physician for Allergy, The Mt. Sinai Hospital, New York. Pp. 156; 8 ills. New York: The Josiah Macy, Jr. Foundation, 1952. Price, $3.25.

KETY from the National Institute of Mental Health defends the thesis that all phenomena of behavior of living organisms are compatible with a mechanistic interpretation. However, he believes that consciousness cannot be explained in terms of physics and chemistry and that it is qualitatively different from matter and energy. Wolberg

from the Department of Psychiatry, New York Medical College, presents the recordings of a hypnoanalytic treatment session of a patient who, during the trance, became aware of certain unconscious aspects of himself hitherto repressed. A motion picture demonstrates a hypnotically induced experimental conflict. Finally the Swiss physiologist Monnier (disciple of Hess, Zürich) reports the affects of electric stimulation in unanesthetized freely moving animals and man. Much space is devoted to the informal discussions that followed the presentation of these papers. These discussions representing a multiprofessional approach give the book its particular flavor and greatly enhance its value. E. S.

STARLING'S PRINCIPLES OF HUMAN PHYSIOLOGY. Edited by SIR CHARLES LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D., Emeritus Professor of Physiology, University of London. 11th ed. Pp. 1210; 709 ills., some in color. Philadelphia: Lea & Febiger, 1952. Price, $11.00.

FOR over 40 years, Starling's Principles of Human Physiology has maintained its position in the front rank of standard texts. The present edition is the 11th, and the 7th in which the present editor, Sir Charles Lovatt Evans, has participated. All teachers and students of the subject will welcome this revised text. R. K.

ENTWICKLUNGSGESCHICHTE PHYSIOLOGISCHER PROBLEMS IN TABELLEN FORM. By K. E. ROTHSCHUH, a.o. Professor Physiolog. Inst. Univ. Munster. Pp. VIII, 122; no ills. Munich: Urban and Schwarzenberg, 1952. Price, 16 DM (Paper).

THIS booklet presenting the development of physiology in tabular form contains a rich list of 2170 references divided into 18 classes such as Blood, Respiration, Heart, Blood Circulation and Regulation, Energy Exchange, Temperature Regulation. These are further subdivided, the Blood, for instance, into 6 groups. The book, however, has various shortcomings, especially for English speaking readers. References to works in English are extremely few, perhaps explained by the author's use of only one reference book in English; granted that a rigorous selection was necessitated to keep within bounds, those chosen often give a very lopsided picture if unsupported. This very lopsidedness, on the other hand, is an advantage for non-Germans who have other reference tables to work with, as room is gained for references to many German works that might otherwise be uncovered with difficulty. If used as an accessory to such works as Hirsch's Biographisches Lexikon, Kelly's Encyclopedia of Medical Sources (1948), the chronological table in Garrison's History and P. D. White's chronological table of heart discoveries, it can well prove useful and is therefore recommended even to non-German readers. E. K.

UNIPOLAR LEAD ELECTROCARDIOGRAPHY AND VECTORCARDIOGRAPHY. By EMANUEL GOLDBERGER, M.D., F.A.C.P., Associate Attending Physician, Montefiore Hospital, New York. 3rd ed. Pp. 601; 301 ills. Philadelphia: Lea & Febiger, 1953. Price, $10.00.

THE publication of a third edition is adequate testimony of the popularity of Goldberger's book. His book was the first to appear based upon the brilliant synthetic interpretation of the electrocardiogram developed by Wilson. He has, however, extended Wilson's concepts by a simple and apparently logical interpretation of the Q wave. This interpretation is given in a persuasively dogmatic fashion.

No evidence is submitted to substantiate his interpretations. Nor is the utility of his classification demonstrated. His interpretation assumes a one to one relationship between the electrical and anatomic position of the heart in health and disease. It ignores the effects of balancing potentials and the size of each chamber.

A new section is devoted to vectorcardiography. The vectorcardiograms are crudely derived (he admits) from conventional electrocardiograms so that abnormalities clearly seen in the latter (p. 552) are not recognizable in the former. Such a derivation is justified if a new synthesis or approach is developed which presumably is superior in interpretation. But Goldberger interprets his derived vectorcardiogram on the basis of the electrocardiographic leads from which it was obtained. L. S.

NEW BOOKS

Estimated World Requirements of Narcotic Drugs in 1953. United Nations, Geneva. Pp. 59. New York: Columbia University Press, 1952. Price, $.50.

Biologisch - Medizinisches Taschenjahrbuch, 1953. By DR. MED. HANS HAFERKAMP. Pp. 508. Stuttgart: Hippokrates-Verlag Marquardt & Cie, 1953. Price, DM 7.50.

Second Annual Report on Stress. By HANS SELYE, M.D., PH.D. (PRAGUE), D.SC. (MCGILL) and ALEXANDER HORAVA, M.D., University of Montreal. Pp. 526; 65 ills. Montreal: Acta, Inc., 1952. Price, $10.00.

THE 1952 annual report on Stress includes over 4,000 references covering many related phenomena. This book, in contrast to the preceding one, does not summarize the important contributions but merely lists them for reference purposes. The former format was more valuable to the reader, but the present technique is still of great help to workers in the field. W. P.

Employment Problems of Disabled Youth in Glasgow. By T. FERGUSON, A. N. MACPHAIL AND MARGARET I. MCVEAN. Pp. 66. London: H. M. Stationery Office, 1952. Price, 3 shillings.

The Superego. By EDMUND BERGLER, M.D. Pp. 367. New York: Grune & Stratton, 1952. Price, $6.75.

THIS is a book on the nature of conscience by a psychoanalyst who has written extensively on the neuroses, and has a previous book on the same subject entitled, "The Battle of the Conscience." He points out the importance of making the unconscious conscious: the tyranny of the Superego and the unconscious tendency of man to punish himself. This is primarily a book for the specialist doing psychiatric therapy. O. E.

Rare Manifestations of Metabolic Bone Disease. By I. SNAPPER, M.D. Pp. 93; 18 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $3.00.

THIS small text is excellent. The introductory notes on osteogenesis and calcium metabolism can be readily understood by the clinician. The bulk of the remainder of the book describes very well hyperparathyroidism and multiple myeloma. Paget's disease is briefly touched upon.

This text belongs on the shelf of every medical student, orthopedist and certainly the internist, who many times sees the patient initially and has to consider metabolic disease in general as a possible cause of the presenting complaint. A. S.

1953 Medical Progress. A Review of Medical Advances During 1952. Edited by MORRIS FISHBEIN, M.D. Pp. 301. New York: The Blakiston Co., 1953. Price, $5.00.

THE desire of good doctors for keeping abreast of medical advances and the difficulty of busy doctors in finding time to do so, have created a demand for books of the nature of summaries of medical news. This one is somewhat different from the others. Rather than choosing a particular branch of medicine, it attempts to cover the entire field. Various individuals, each of outstanding reputation, present brief and informal reports of recent advances in their respective specialties. The reading is easy, the style uniform. It is recommended to the busy doctor. J. Z.

L'Hérédité Humaine. By JEAN ROSTAND. Pp. 126; 12 ills. Paris: Presses Universitaires de France, 1952. Price, not given.

Les Glandes Endocrines. By RAYMOND KEHL, D.SC., M.D. Pp. 126; 2 ills. Paris: Presses Universitaires de France, 1952. Price, not given.

THE University Presses of France publish a series of little paper-covered pocket-sized volumes over a wide range of subjects. The number of the publications now approaches 600. Many are on medical subjects.

No. 550 deals with human heredity and presents a concise outline of current knowledge on this subject. The author is a recognized authority in the field. The coverage of material is reasonably good.

No. 553 is an outline of current knowledge of endocrine function. Unfortunately, the field is so large that the attempt to cover it even in the barest outline form within the compass of this booklet proves quite inadequate. R. K.

Synovial Fluid Changes in Joint Disease. By MARIAN W. ROPES, M.D., and WALTER BAUER, M.D., Massachusetts General Hospital and Harvard Medical School. Pp. 150; 15 ills. Cambridge, Mass.: Harvard University Press, 1953. Price, $4.00.

THE authors recount in detail their studies, extending over a period of 20 years, of the chemical and cellular alterations of joint fluid in health and in disease. This volume is of special interest to the investigator of fundamental alterations in joint physiology. The fact that the clinical application of the facts so painfully acquired is quite limited should stimulate rather than retard interest in the further study of joint fluid. J. L.

Problems of Infancy and Childhood. Transactions of the Sixth Conference, March 17 and 18, 1952. Edited by MILTON J. E. SENN, M.D., Professor of Pediatrics, Yale School of Medicine. Pp. 166; 1 ill. New York: Josiah Macy, Jr. Foundation, 1953. Price, $2.50.

THIS book contains the four papers and the edited discussion of the twenty-six participants of the sixth conference on Problems of Infancy and Childhood sponsored by the Macy Foundation.

The four papers: (1) Emotional Development in the First Year of Life (Escalona); (2) A Brief Review of W.H.O. Activities (Kjellberg); (3) Observation of Individual Tendencies in the First Year of Life (Wolf); and (4) Excessive Crying in Infants —A Family Disease (Stewart).

The transactions will be of interest to active workers in the behavior field not only for the content of the papers but particularly for the discussion of them. W. N.

NEW EDITIONS

Clinical Diagnosis by Laboratory Methods. By JAMES CAMPBELL TODD, PH.B., M.D., ARTHUR HAWLEY SANFORD, A.M., M.D., and BENJAMIN B. WELLS, M.D., PH.D. 12th ed. Pp. 998; 403 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $8.50.

CLINICIANS will welcome the 12th edition of this well-established standard text. There is a new co-author, Doctor Wells. The subject matter in this rapidly advancing field has been revised and brought up-to-date. R. K.